Published in final edited form as:

Biochem Soc Trans. 2016 February ; 44(1): 293–298. doi:10.1042/BST20150229.

Phosphoinositide signalling in type 2 diabetes: a β-cell perspective

Lucia E. Rameh[*,1], **Jude T. Deeney**[*]

* Department of Medicine, Boston University School of Medicine, 650 Albany Street, Boston, MA 02118, U.S.A.

Abstract

Type 2 diabetes is a complex disease. It results from a failure of the body to maintain energy homoeostasis. Multicellular organisms have evolved complex strategies to preserve a relatively stable internal nutrient environment, despite fluctuations in external nutrient availability. This complex strategy involves the co-ordinated responses of multiple organs to promote storage or mobilization of energy sources according to the availability of nutrients and cellular bioenergetics needs. The endocrine pancreas plays a central role in these processes by secreting insulin and glucagon. When this co-ordinated effort fails, hyperglycaemia and hyperlipidaemia develops, characterizing a state of metabolic imbalance and ultimately overt diabetes. Although diabetes is most likely a collection of diseases, scientists are starting to identify genetic components and environmental triggers. Genome-wide association studies revealed that by and large, gene variants associated with type 2 diabetes are implicated in pancreatic β-cell function, suggesting that the β-cell may be the weakest link in the chain of events that results in diabetes. Thus, it is critical to understand how environmental cues affect the β-cell. Phosphoinositides are important 'decoders' of environmental cues. As such, these lipids have been implicated in cellular responses to a wide range of growth factors, hormones, stress agents, nutrients and metabolites. Here we will review some of the well-established and potential new roles for phosphoinositides in β-cell function/dysfunction and discuss how our knowledge of phosphoinositide signalling could aid in the identification of potential strategies for treating or preventing type 2 diabetes.

Keywords

β-cell; insulin; lipid kinases; nutrients; obesity; signalling

Phosphoinositides in nutrient-stimulated insulin secretion

β-cells play an essential role in maintaining energy homoeostasis by secreting insulin in response to plasma glucose and other nutrients. The widely accepted model for describing the mechanisms by which glucose stimulates insulin secretion claims that glucose metabolism gives rise to both triggering and amplifying signals that regulate insulin exocytosis [1]. Metabolic signals lead to ATP-sensitive K^+ (K_{ATP}) channel closure, membrane depolarization and Ca^{2+} entry through voltage-operated Ca^{2+} channels (VOCC).

1 To whom correspondence should be addressed (rameh@bu.edu).

A rise in intracellular Ca^{2+} ultimately triggers exocytosis of primed insulin granules. Amplifying signals enhance insulin released through the triggering pathway and thus require elevated Ca^{2+} . In addition, there are other metabolic signals that defy these categories by stimulating insulin release in the absence of elevated Ca^{2+} , including H_2O_2 [2] mono-acyl-glycerol (MAG) [3,4] and long-chain acyl-CoA (LC-CoA) [5].

Exposure to glucose and other secretagogues results in pulsatile insulin release and stimulates dramatic oscillations in phosphoinositide metabolism in the plasma membrane of the β-cell, as measured by quantitative imaging of the translocation of phosphoinositide-binding probes [6–8]. These oscillations are the result of dynamic phosphorylation, dephosphorylation and breakdown of phosphoinositides and are poised to influence the cellular response to nutrients, by (i) recruitment of signalling proteins containing phosphoinositide-binding domains; (ii) generation of soluble inositol second messengers and (iii) direct regulation of trans-membrane proteins containing polybasic residues.

PtdIns(4,5)P_2, one of the most abundant phosphoinositides in cells, regulates vesicle budding, fusion and actin rearrangements involved in vesicle transport [9]. PtdIns(4,5)P_2 can bind to PH and C2 domains to regulate the localization or function of various proteins [10]. Recently PtdIns(4,5)P_2 was found to aggregate at sites in the plasma membrane, reaching an estimated lipid density of up to 82%. This high density of PtdIns(4,5)P_2 is achieved at specific membrane microdomains of approximately 73 nm in size, allowing attraction of syntaxin and docking of secretory granules [11]. PtdIns(4,5)P_2 can also bind to synaptotagmin through its C2 domain, increasing its Ca^{2+} sensitivity and reducing the Ca^{2+} threshold for exocytosis [12]. In addition, PtdIns(4,5)P_2 binds CAPS (calcium-dependent activator protein for secretion) through its PH domain, which potentiates exocytosis (for a review [13]). Thus, by recruiting proteins that contain phosphoinositide-binding modules (e.g. PH, C2, PX domains), phosphoinositides act as nucleators of effector molecules on to specific submembrane regions [14].

PtdIns(4,5)P_2 can generate other signalling molecules that are involved in the regulation of glucose-stimulated insulin secretion (GSIS). High Ca^{2+} for instance, activates PLC to hydrolyse PtdIns(4,5)P_2 yielding diacylglycerol (DAG) and Ins(1,4,5)P_3. DAG increases secretion by binding MUNC-13 [15] and Ins(1,4,5)P_3 amplifies the triggering signal by mobilizing intracellular Ca^{2+} stores [16]. Ins(1,4,5)P_3-sensitive stores have been implicated in GSIS [17] and in the replenishment of mature insulin granules [18]. Ins(1,4,5)P_3 is also a precursor for other inositol polyphosphates (e.g. Ins(3,4,5,6)P_4 and IP_6) and inositol pyrophosphates (e.g. IP_7 and IP_8) that are involved in the regulation of insulin secretion (for a thorough review, refer to [19]). Thus, PtdIns(4,5)P_2 role in exocytosis may depend on the intracellular Ca^{2+} concentration. For instance, when Ca^{2+} is low PtdIns(4,5)P_2 may bind directly to CAPS to stimulate secretion, but when Ca^{2+} is high it may be broken down to generate DAG and Ins(1,4,5)P_3 [15].

Additionally, PtdIns(4,5)P_2 was found to bind and regulate the K_{ATP} channel, which is a complex of four Kir6.2 subunits and four SUR (sulphonylurea receptor) subunits. PtdIns(4,5)P_2 interaction with Kir6.2 promotes opening of the channel (which decreases insulin secretion) and reduces the inhibition by ATP [20]. Mutations in Kir6.2 that result in

impaired PtdIns(4,5)P_2 binding to this channel have been associated with hyperinsulinism due to increased β-cell excitability [20,21]. It is not entirely clear how changes in PtdIns(4,5)P_2 metabolism contributes to the regulation of insulin secretion *in vivo*, however, it is likely that physiological responses will require local synthesis and/or consumption of PtdIns(4,5)P_2, rather than global changes.

Phosphoinositide kinases in β-cell function

The effect of cellular phosphoinositides on β-cell function has been addressed by manipulating the expression or catalytic activity of the enzymes involved in phosphoinositide synthesis or consumption, i.e. phosphoinositide kinases, phosphatases and lipases. In addition, cellular phosphoinositides can be 'neutralized' by using overexpression of phosphoinositide-binding domains. One common theme that emerged from these studies is that perturbations in phosphoinositide metabolism can disturb the β-cell in multiple ways. For example, several studies have addressed the role of PtdIns(4,5)P_2 in GSIS by manipulating the levels of phosphatidylinositol 4-kinases (PI4K) and phosphatidylinositol-4-phosphate 5-kinases (PIP5Ks), which are enzymes responsible for generating the bulk of PtdIns(4,5)P_2 in cells [9], and/or by overexpression of the PLCδ PH domain, which specifically binds to plasma membrane PtdIns(4,5)P_2. In some cases, decreasing PtdIns(4,5)P_2 in β-cells impaired secretion [22–24], indicating a positive role for this lipid in insulin release. In others, forced increase in PtdIns(4,5)P_2 levels through overexpression of PIP5K inhibited secretion [21,25], indicating a negative role for PtdIns(4,5)P_2 in GSIS. Whereas the positive effects of PtdIns(4,5)P_2 on insulin secretion can be explained by the ability of this lipid to regulate insulin granule maturation and exocytosis [22–24,26], the negative effect was attributed to PtdIns(4,5)P_2-dependent decrease in ATP sensitivity of the K_{ATP} channel [21]. Interestingly, in one study, RNAi-mediated knockdown of PIP5Kα in β-cells, which reduced plasma membrane PtdIns(4,5)P_2 without affecting Ins(1,4,5)P_3 levels, led to a significant increase in basal insulin secretion, but a decrease in fold GSIS over basal [26].

It is important to emphasize that overexpression/knockdown of PIP5K results in global changes in PtdIns(4,5)P_2. In contrast, overexpression/knockdown of the phosphatidylinositol-5-phosphate 4-kinases (PIP4Ks), which catalyse the phosphorylation of PtdIns5P into PtdIns(4,5)P_2, only affects a minor fraction of cellular PtdIns(4,5)P_2 [27]. However, the role of this subpopulation of PtdIns(4,5)P_2 in GSIS has not been examined. Future studies in which only local levels of PtdIns(4,5)P_2 are manipulated will be essential to identify the role of specific pools of phosphoinositides in β-cell function. One promising strategy to address this issue is the use of recently developed optogenetic tools, which allow the manipulation of local levels of PtdIns(4,5)P_2 through light-dependent recruitment of phosphatases or kinases to well-delineated regions of the plasma membrane [28].

Phosphoinositide 3-kinases (PI3Ks) and the lipid products that they generate, e.g. PtdIns3P, PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3, have also been implicated in GSIS. This family of enzymes is divided into class IA, class IB, class II and class III [29]. Initial studies using the PI3Ks inhibitors, wortmannin and Ly294002, revealed a potential negative role for these kinases in GSIS [30–33], but a positive role in glucagon-like peptide-1 (GLP-1)-enhanced

insulin secretion [34]. The role of specific pools of PI3K lipids is now being examined through deletion of individual isoforms of PI3K in the β-cell. Suppression of class IA PI3K through knockdown of the catalytic subunits (p110) in β-cells revealed that p110α and p110β had opposing roles in GSIS [35], with p110α deletion increasing GSIS and the p110β impairing GSIS through a mechanism that did not require its catalytic activity. Suppression of class IB (p110γ isoform), which is activated through G-protein coupled receptors, resulted in decreased actin depolarization and insulin granule recruitment to the plasma membrane, and consequently decreased GSIS in mice or in isolated islets [36,37]. Deletion of the gene for the class IA PI3K regulatory subunit (p85α) specifically in β-cells, alone or in conjunction with systemic deletion of the gene for p85β, impaired GSIS in mouse, probably due to FOXO-dependent transcriptional changes, which negatively affected the exocytic machinery and promoted loss of β-cell mass [38]. Interestingly, single deletion of the p85α in β-cells had a protective role against endoplasmic reticulum stress that leads to β-cell loss in a mouse model with a mutant insulin gene ($Akita^{-/+}$) [39]. These seemingly contradictory roles of phosphoinositide kinases can be partially explained by short-term compared with long-term effects of the various manipulations. In the short term, PI3K lipids may affect local events involved in actin cytoskeleton remodelling and exocytosis, whereas long-term effects may involve activation of signalling cascades that result in transcriptional reprogramming and metabolic adaptations of the β-cell, as discussed below.

Knockdown of PI3K class II, which generates PtdIns3*P* or PtdIns(3,4)P_2, inhibited GSIS by interfering with late steps in the exocytosis of insulin granules, possibly by inhibiting SNAP25 proteolysis which is necessary for insulin granule fusion [40]. In another study where PI3K class II was knocked down in the β-cell, the authors attributed the decrease in GSIS to transcriptional changes involving PI3KIIα-mediated activation of Akt signalling [41]. Interestingly, expression of class II PI3K is reduced in islets from patients with type 2 diabetes [40].

Class III PI3Ks are the main source of cellular PtdIns3*P*, which is essential for autophagosome biogenesis. It is well established that class III PI3Ks regulate autophagy, a process that is critical for the maintenance of β-cell homoeostasis and function [42–44]. This implicates class III PI3Ks as important players in the maintenance of β-cell mass and glucose homoeostasis, but this remains to be tested. In contrast, class I PI3K signalling inhibits autophagy through TORC1 (target of rapamycin complex 1)-dependent phosphorylation of ULK1 (Unc51-like kinase-1). In fact, a recent study presented evidence that TORC1-mediated inhibition of autophagy could be a mechanism for maintaining low basal insulin secretion upon β-cell starvation [45].

Together, these studies highlight the complexity of the phosphoinositide role in controlling essential steps in the regulation of GSIS and the need to carefully dissect which enzymes are involved in the generation/removal of particular pools of phosphoinositides in β-cells exposed to different environmental cues.

Phosphoinositide signalling in response to excess nutrients

Excess of nutrients is an environmental factor linked to obesity and diabetes [46]. The mobilization of energy sources through metabolism results in the formation of reactive oxygen species (ROS), which have significant impact on phosphoinositide metabolism [47]. For instance, ROS can increase phosphoinositide generation and decrease degradation by inhibiting protein tyrosine phosphatases that turn off receptor signalling and by inhibiting phosphoinositide phosphatases, respectively [48,49]. Although ROS participates in physiological responses, chronic exposure to high levels of nutrients can result in metabolic stress, when excessive production of ROS surpasses the antioxidant capacity of the cell [50]. These pathological levels of ROS can be detrimental to cells. The pancreatic β-cell is particularly susceptible to increases in ROS levels due to lower antioxidant capacity [51]. The metabolic stress ensued by diet-induced obesity in humans and in mice models is accompanied by hyperinsulinaemia. Chronic exposure of β-cells to elevated glucose and fatty acids leads to accumulation of intracellular lipids, increased ROS [52] and plasma membrane cholesterol [53] and results in basal insulin hypersecretion, ultimately causing impaired GSIS [4,54,55]. It is likely that pathological levels of ROS leads to increased generation of PtdIns(4,5)P_2, through inhibition of phosphatases. Furthermore, ROS activates stress pathways that lead to p38 MAPkinase activation and regulation of PIP4K [56]. Cholesterol, in addition to affecting membrane fluidity, inhibits PtdIns(4,5)P_2 hydrolysis and, thus increases the level of PtdIns(4,5)P_2 in the membrane [57]. Thus, it is likely that excess nutrients through increases in ROS or cholesterol affects the levels of cellular PtdIns(4,5)P_2, which could partially explain the changes in insulin secretion in metabolically stressed β-cells. Interestingly, serum cholesterol is increased in many patients with type 2 diabetes.

Phosphoinositide signalling in β-cell expansion and dysfunction

High demand for insulin, such as in obesity or insulin resistance, can signal for β-cell expansion and islet hyperplasia. In this process, phosphoinositides generated by PI3K play a critical role by stimulating downstream pathways that signal for increase in cell proliferation, mass and survival through activation of Akt [58,59]. β-cells with deletion of the genes for insulin and IGF1 receptors had impaired Akt activation, which resulted in increased apoptosis, decreased cell proliferation and loss of β-cell mass in mice [60]. On the other hand, mice with β-cell-specific deletion of PTEN, which is a phosphatase for PI3K lipids, showed islet hyperplasia and increased β-cell size [61]. Rapamycin treatment of an obese rat model prevented β-cell adaptation to hyperglycaemia by reducing β-cell mass and decreasing insulin biosynthesis and secretion [62]. Rapamycin inhibits TORC1 activation downstream of Akt. TORC1, a multimeric kinase complex involved in the regulation of anabolic process that control cell mass and proliferation, is activated in response to growth factors, nutrients and energy availability [63]. The PI3K lipids PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 promote AKT activation and subsequent phosphorylation and inactivation of Tsc1/Tsc2 (tuberousclerosis complex 1 and 2), which are negative regulators of TORC1. In diseases where Tsc1/Tsc2 are inactivated, TORC1 is constitutively active and can signal in the absence of growth factors. TORC1, through the phosphorylation of several regulators of protein translation such as p70S6K, eIF4G and 4E-BP, promotes the translation of

a subset of mRNAs, some of which are themselves regulators of ribosome biogenesis [64]. Thus, TORC1 is a metabolic sensor and master regulator of the protein translational machinery, which signals for improved translational potential in times of high demand for protein synthesis [65]. When TORC1 was activated specifically in β-cells by tissue-specific knockout of Tsc1/Tsc2 or overexpression of Rheb, a positive regulator of TORC1, mice developed islet hyperplasia due to β-cell mass expansion [66–71], which is consistent with a role for TORC1 on anabolic processes. However, these mice also developed hyperinsulinaemia in fasting or fed states, strongly indicating that TORC1 signalling can promote insulin release. In one study, hyperinsulinaemia eventually caused β-cell failure and apoptosis, which culminated in hyperglycaemia and diabetes [67]. Consistent with a role for TORC1 signalling in hyperinsulinaemia, the p70S6K knockout mice were found to be hypoinsulinaemic and resistant to diet-induced obesity [72], and overexpression of a constitutively active p70S6K mutant in β-cells improved insulin secretion [73] (for a comprehensive review refer to [70]). Thus, these studies indicate that increases in TORC1 activity in response to high demand for insulin production may eventually lead to β-cell dysfunction through stimulus-secretion uncoupling.

Concluding remarks

Phosphoinositides have profound effects on β-cell function, yet much more work needs to be done to uncover how specific pools are regulated in response to changes in the nutrient environment and how they may delay or promote the development of diabetes. Given that the ultimate response to changes in cellular phosphoinositides in the β-cell will depend on the location and context in which they are operating, a first step will be to identify strategies to regulate a specific pool of phosphoinositide, without affecting others. There is also a great need to validate the knowledge acquired using intact islets in their natural environment, rather than cultured β-cells.

A new generation of inhibitors that specifically target certain isoforms of phosphoinositide kinases is being rapidly developed, with some already in clinical trials for the treatment of various cancers. These could be used as tools to better predict the short-term effects of different pools of phosphoinositides in β-cell function in animals. Importantly, because phosphoinositides may have positive and negative effects on insulin secretion, it will be critical to evaluate the effects of such inhibitors on glucose homoeostasis in patients. With better knowledge on the impact of PI-kinases in the β-cell, we should be able to design better strategies for treating cancers or diabetes without compromising β-cell health. Such strategies may turn out to be potent therapies for preventing or even reversing the process of β-cell dysfunction.

Acknowledgements

We thank Dr Robin Irvine from The Babraham Institute for his work, his dedication to science and his inspiration to many scientists. We would like to thank our collaborators Dr Barbara Corkey (BEC) from BUSM and Drs Agata Jurczyk and Rita Bortell from University of Massachusetts Medical School for insightful discussions and support.

Funding

This work was supported by the National Institutes of Health [grant number R01 DK 063219 (to L.E.R.) and grant number R01 DK35914 (to B.E.C.)].

Abbreviations:

CAPS	calcium-dependent activator protein for secretion
DAG	diacylglycerol
GSIS	glucose-stimulated insulin secretion
MAG	mono-acyl-glycerol
PI3K	Phosphoinositide 3-kinase
PIP5K	phosphatidylinositol-4-phosphate 5-kinase
PIP4K	phosphatidylinositol-5-phosphate 4-kinase
ROS	reactive oxygen species
SUR	sulphonylurea receptor
TORC1	target of rapamycin complex 1

References

1. MacDonald PE, Joseph JW and Rorsman P (2005) Glucose-sensing mechanisms in pancreatic beta-cells. Philos. Trans. R. Soc. Lond. B Biol. Sci 360, 2211–2225 [PubMed: 16321791]
2. Pi J, Bai Y, Zhang Q, Wong V, Floering LM, Daniel K, Reece JM, Deeney JT, Andersen ME, Corkey BE and Collins S (2007) Reactive oxygen species as a signal in glucose-stimulated insulin secretion. Diabetes 56, 1783–1791 [PubMed: 17400930]
3. Zhao S, Mugabo Y, Iglesias J, Xie L, Delghingaro-Augusto V, Lussier R, Peyot ML, Joly E, Taib B, Davis MA et al. (2014) alpha/beta-Hydrolase domain-6-accessible monoacylglycerol controls glucose-stimulated insulin secretion. Cell Metab. 19, 993–1007 [PubMed: 24814481]
4. Saadeh M, Ferrante TC, Kane A, Shirihai O, Corkey BE and Deeney JT (2012) Reactive oxygen species stimulate insulin secretion in rat pancreatic islets: studies using mono-oleoyl-glycerol. PloS One 7, e30200 [PubMed: 22272304]
5. Deeney JT, Gromada J, Hoy M, Olsen HL, Rhodes CJ, Prentki M, Berggren PO and Corkey BE (2000) Acute stimulation with long chain acyl-CoA enhances exocytosis in insulin-secreting cells (HIT T-15 and NMRI beta-cells). J. Biol. Chem 275, 9363–9368 [PubMed: 10734079]
6. Hagren OI and Tengholm A (2006) Glucose and insulin synergistically activate phosphatidylinositol 3-kinase to trigger oscillations of phosphatidylinositol 3,4,5-trisphosphate in beta-cells. J. Biol. Chem 281, 39121–39127 [PubMed: 17074763]
7. Thore S, Wuttke A and Tengholm A (2007) Rapid turnover of phosphatidylinositol-4,5-bisphosphate in insulin-secreting cells mediated by Ca2 + and the ATP-to-ADP ratio. Diabetes 56, 818–826 [PubMed: 17327453]
8. Wuttke A, Idevall-Hagren O and Tengholm A (2010) Imaging phosphoinositide dynamics in living cells. Methods Mol. Biol 645, 219–235 [PubMed: 20645191]
9. Sun Y, Thapa N, Hedman AC and Anderson RA (2013) Phosphatidylinositol 4,5-bisphosphate: targeted production and signaling. BioEssays 35, 513–522 [PubMed: 23575577]
10. Di Paolo G and De Camilli P (2006) Phosphoinositides in cell regulation and membrane dynamics. Nature 443, 651–657 [PubMed: 17035995]

11. van den Bogaart G, Meyenberg K, Risselada HJ, Amin H, Willig KI, Hubrich BE, Dier M, Hell SW, Grubmuller H, Diederichsen U and Jahn R (2011) Membrane protein sequestering by ionic protein-lipid interactions. Nature 479, 552–555 [PubMed: 22020284]
12. van den Bogaart G, Meyenberg K, Diederichsen U and Jahn R (2012) Phosphatidylinositol 4,5-bisphosphate increases Ca2 + affinity of synaptotagmin-1 by 40-fold. J. Biol. Chem 287, 16447–16453 [PubMed: 22447935]
13. Martin TF (2015) PI(4,5)P(2)-binding effector proteins for vesicle exocytosis. Biochim. Biophys. Acta 1851, 785–793 [PubMed: 25280637]
14. Balla T (2005) Inositol-lipid binding motifs: signal integrators through protein-lipid and protein-protein interactions. J. Cell. Sci 118, 2093–2104 [PubMed: 15890985]
15. Kabachinski G, Yamaga M, Kielar-Grevstad DM, Bruinsma S and Martin TF (2014) CAPS and Munc13 utilize distinct PIP2-linked mechanisms to promote vesicle exocytosis. Mol. Biol. Cell 25, 508–521 [PubMed: 24356451]
16. Berridge MJ and Irvine RF (1989) Inositol phosphates and cell signalling. Nature 341, 197–205 [PubMed: 2550825]
17. Ye R, Ni M, Wang M, Luo S, Zhu G, Chow RH and Lee AS (2011) Inositol 1,4,5-trisphosphate receptor 1 mutation perturbs glucose homeostasis and enhances susceptibility to diet-induced diabetes. J. Endocrinol 210, 209–217 [PubMed: 21565852]
18. Gromada J, Hoy M, Renstrom E, Bokvist K, Eliasson L, Gopel S and Rorsman P (1999) CaM kinase II-dependent mobilization of secretory granules underlies acetylcholine-induced stimulation of exocytosis in mouse pancreatic B-cells. J. Physiol 518 (Pt 3), 745–759 [PubMed: 10420011]
19. Barker CJ and Berggren PO (2013) New horizons in cellular regulation by inositol polyphosphates: insights from the pancreatic beta-cell. Pharmacol. Rev 65, 641–669 [PubMed: 23429059]
20. Logothetis DE, Petrou VI, Zhang M, Mahajan R, Meng XY, Adney SK, Cui M and Baki L (2015) Phosphoinositide control of membrane protein function: a frontier led by studies on ion channels. Annu. Rev. Physiol 77, 81–104 [PubMed: 25293526]
21. Lin CW, Yan F, Shimamura S, Barg S and Shyng SL (2005) Membrane phosphoinositides control insulin secretion through their effects on ATP-sensitive K + channel activity. Diabetes 54, 2852–2858 [PubMed: 16186385]
22. Lawrence JT and Birnbaum MJ (2003) ADP-ribosylation factor 6 regulates insulin secretion through plasma membrane phosphatidylinositol 4,5-bisphosphate. Proc. Natl. Acad. Sci. U.S.A 100, 13320–13325 [PubMed: 14585928]
23. Olsen HL, Hoy M, Zhang W, Bertorello AM, Bokvist K, Capito K, Efanov AM, Meister B, Thams P, Yang SN et al. (2003) Phosphatidylinositol 4-kinase serves as a metabolic sensor and regulates priming of secretory granules in pancreatic beta cells. Proc. Natl. Acad. Sci. U.S.A 100, 5187–5192 [PubMed: 12700357]
24. Waselle L, Gerona RR, Vitale N, Martin TF, Bader MF and Regazzi R (2005) Role of phosphoinositide signaling in the control of insulin exocytosis. Mol. Endocrinol 19, 3097–3106 [PubMed: 16081518]
25. Tomas A, Yermen B, Regazzi R, Pessin JE and Halban PA (2010) Regulation of insulin secretion by phosphatidylinositol-4,5-bisphosphate. Traffic 11, 123–137 [PubMed: 19845918]
26. Zhang J, Luo R, Wu H, Wei S, Han W and Li G (2009) Role of type Ialpha phosphatidylinositol-4-phosphate 5-kinase in insulin secretion, glucose metabolism, and membrane potential in INS-1 beta-cells. Endocrinology 150, 2127–2135 [PubMed: 19116346]
27. Rameh LE, Tolias KF, Duckworth BC and Cantley LC (1997) A new pathway for synthesis of phosphatidylinositol-4,5-bisphosphate [see comments]. Nature 390, 192–196 [PubMed: 9367159]
28. Idevall-Hagren O and Decamilli P (2014) Manipulation of plasma membrane phosphoinositides using photoinduced protein-protein interactions. Methods Mol. Biol 1148, 109–128
29. Fruman DA, Meyers RE and Cantley LC (1998) Phosphoinositide kinases. Annu. Rev. Biochem 67, 481–507 [PubMed: 9759495]
30. Collier JJ, White SM, Dick GM and Scott DK (2004) Phosphatidylinositol 3-kinase inhibitors reveal a unique mechanism of enhancing insulin secretion in 832/13 rat insulinoma cells. Biochem. Biophys. Res. Commun 324, 1018–1023 [PubMed: 15485656]

31. Eto K, Yamashita T, Tsubamoto Y, Terauchi Y, Hirose K, Kubota N, Yamashita S, Taka J, Satoh S, Sekihara H et al. (2002) Phosphatidylinositol 3-kinase suppresses glucose-stimulated insulin secretion by affecting post-cytosolic [Ca(2+)] elevation signals. Diabetes 51, 87–97 [PubMed: 11756327]
32. Nunoi K, Yasuda K, Tanaka H, Kubota A, Okamoto Y, Adachi T, Shihara N, Uno M, Xu LM, Kagimoto S et al. (2000) Wortmannin, a PI3-kinase inhibitor: promoting effect on insulin secretion from pancreatic beta cells through a cAMP-dependent pathway. Biochem. Biophys. Res. Commun 270, 798–805 [PubMed: 10772905]
33. Hagiwara S, Sakurai T, Tashiro F, Hashimoto Y, Matsuda Y, Nonomura Y and Miyazaki J (1995) An inhibitory role for phosphatidylinositol 3-kinase in insulin secretion from pancreatic B cell line MIN6. Biochem. Biophys. Res. Commun 214, 51–59 [PubMed: 7669052]
34. MacDonald PE, Wang X, Xia F, El-kholy W, Targonsky ED, Tsushima RG and Wheeler MB (2003) Antagonism of rat beta-cell voltage-dependent K + currents by exendin 4 requires dual activation of the cAMP/protein kinase A and phosphatidylinositol 3-kinase signaling pathways. J. Biol. Chem 278, 52446–52453 [PubMed: 14565957]
35. Kolic J, Spigelman AF, Plummer G, Leung E, Hajmrle C, Kin T, Shapiro AM, Manning Fox JE and MacDonald PE (2013) Distinct and opposing roles for the phosphatidylinositol 3-OH kinase catalytic subunits p110alpha and p110beta in the regulation of insulin secretion from rodent and human beta cells. Diabetologia 56, 1339–1349 [PubMed: 23568272]
36. MacDonald PE, Joseph JW, Yau D, Diao J, Asghar Z, Dai F, Oudit GY, Patel MM, Backx PH and Wheeler MB (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 [PubMed: 15231713]
37. Pigeau GM, Kolic J, Ball BJ, Hoppa MB, Wang YW, Ruckle T, Woo M, Manning Fox JE and MacDonald PE (2009) Insulin granule recruitment and exocytosis is dependent on p110gamma in insulinoma and human beta-cells. Diabetes 58, 2084–2092 [PubMed: 19549714]
38. Kaneko K, Ueki K, Takahashi N, Hashimoto S, Okamoto M, Awazawa M, Okazaki Y, Ohsugi M, Inabe K, Umehara T et al. (2010) Class IA phosphatidylinositol 3-kinase in pancreatic beta cells controls insulin secretion by multiple mechanisms. Cell Metab 12, 619–632 [PubMed: 21109194]
39. Winnay JN, Dirice E, Liew CW, Kulkarni RN and Kahn CR (2014) p85alpha deficiency protects beta-cells from endoplasmic reticulum stress-induced apoptosis. Proc. Natl. Acad. Sci. U.S.A 111, 1192–1197 [PubMed: 24395790]
40. Dominguez V, Raimondi C, Somanath S, Bugliani M, Loder MK, Edling CE, Divecha N, da Silva-Xavier G, Marselli L, Persaud SJ et al. (2011) Class II phosphoinositide 3-kinase regulates exocytosis of insulin granules in pancreatic beta cells. J. Biol. Chem 286, 4216–4225 [PubMed: 21127054]
41. Leibiger B, Moede T, Uhles S, Barker CJ, Creveaux M, Domin J, Berggren PO and Leibiger IB (2010) Insulin-feedback via PI3K-C2alpha activated PKBalpha/Akt1 is required for glucose-stimulated insulin secretion. FASEB J. 24, 1824–1837 [PubMed: 20061534]
42. Kaushik S, Singh R and Cuervo AM (2010) Autophagic pathways and metabolic stress. Diabetes Obesity Metab. 12 Suppl 2, 4–14
43. Las G and Shirihai OS (2010) The role of autophagy in beta-cell lipotoxicity and type 2 diabetes. Diabetes Obesity Metab. 12 (Suppl 2), 15–19
44. Hur KY, Jung HS and Lee MS (2010) Role of autophagy in beta-cell function and mass. Diabetes Obesity Metab. 12 (Suppl 2), 20–26
45. Goginashvili A, Zhang Z, Erbs E, Spiegelhalter C, Kessler P, Mihlan M, Pasquier A, Krupina K, Schieber N, Cinque L et al. (2015) Insulin granules. Insulin secretory granules control autophagy in pancreatic beta cells. Science 347, 878–882 [PubMed: 25700520]
46. Wellen KE and Thompson CB (2010) Cellular metabolic stress: considering how cells respond to nutrient excess. Mol. Cell 40, 323–332 [PubMed: 20965425]
47. Besse-Patin A and Estall JL (2014) An intimate relationship between ROS and Insulin signalling: implications for antioxidant treatment of fatty liver disease. Int. J. Cell Biol 2014, 519153
48. Meng TC, Fukada T and Tonks NK (2002) Reversible oxidation and inactivation of protein tyrosine phosphatases *in vivo*. Mol. Cell 9, 387–399 [PubMed: 11864611]

49. Kwon J, Lee SR, Yang KS, Ahn Y, Kim YJ, Stadtman ER and Rhee SG (2004) Reversible oxidation and inactivation of the tumor suppressor PTEN in cells stimulated with peptide growth factors. Proc. Natl. Acad. Sci. U.S.A 101, 16419–16424 [PubMed: 15534200]
50. Ray PD, Huang BW and Tsuji Y (2012) Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell. Signal 24, 981–990 [PubMed: 22286106]
51. Gehrmann W, Elsner M and Lenzen S (2010) Role of metabolically generated reactive oxygen species for lipotoxicity in pancreatic beta-cells. Diabetes Obesity Metab. 12 (Suppl 2), 149–158
52. Wang X, Li H, De Leo D, Guo W, Koshkin V, Fantus IG, Giacca A, Chan CB, Der S and Wheeler MB (2004) Gene and protein kinase expression profiling of reactive oxygen species-associated lipotoxicity in the pancreatic beta-cell line MIN6. Diabetes 53, 129–140 [PubMed: 14693707]
53. El-Assaad W, Joly E, Barbeau A, Sladek R, Buteau J, Maestre I, Pepin E, Zhao S, Iglesias J, Roche E and Prentki M (2010) Glucolipotoxicity alters lipid partitioning and causes mitochondrial dysfunction, cholesterol, and ceramide deposition and reactive oxygen species production in INS832/13 ss-cells. Endocrinology 151, 3061–3073 [PubMed: 20444946]
54. Segall L, Lameloise N, Assimacopoulos-Jeannet F, Roche E, Corkey P, Thumelin S, Corkey BE and Prentki M (1999) Lipid rather than glucose metabolism is implicated in altered insulin secretion caused by oleate in INS-1 cells. Am. J. Physiol 277, E521–E528 [PubMed: 10484365]
55. Erion KA, Berdan CA, Burritt NE, Corkey BE and Deeney JT (2015) Chronic exposure to excess nutrients left-shifts the concentration dependence of glucose-stimulated insulin secretion in pancreatic beta-cells. J. Biol. Chem 290, 16191–16201 [PubMed: 25934392]
56. Jones DR, Bultsma Y, Keune WJ, Halstead JR, Elouarrat D, Mohammed S, Heck AJ, D'Santos CS and Divecha N (2006) Nuclear PtdIns5P as a transducer of stress signaling: an *in vivo* role for PIP4Kbeta. Mol. Cell 23, 685–695 [PubMed: 16949365]
57. Hao M and Bogan JS (2009) Cholesterol regulates glucose-stimulated insulin secretion through phosphatidylinositol 4,5-bisphosphate. J. Biol. Chem 284, 29489–29498 [PubMed: 19729450]
58. Tuttle RL, Gill NS, Pugh W, Lee JP, Koeberlein B, Furth EE, Polonsky KS, Naji A and Birnbaum MJ (2001) Regulation of pancreatic beta-cell growth and survival by the serine/threonine protein kinase Akt1/PKBalpha. Nat. Med 7, 1133–1137 [PubMed: 11590437]
59. Bernal-Mizrachi E, Wen W, Stahlhut S, Welling CM and Permutt MA (2001) Islet beta cell expression of constitutively active Akt1/PKB alpha induces striking hypertrophy, hyperplasia, and hyperinsulinemia. J. Clin. Invest 108, 1631–1638 [PubMed: 11733558]
60. Ueki K, Okada T, Hu J, Liew CW, Assmann A, Dahlgren GM, Peters JL, Shackman JG, Zhang M, Artner I et al. (2006) Total insulin and IGF-I resistance in pancreatic beta cells causes overt diabetes. Nat. Genet 38, 583–588 [PubMed: 16642022]
61. Nguyen KT, Tajmir P, Lin CH, Liadis N, Zhu XD, Eweida M, Tolasa-Karaman G, Cai F, Wang R, Kitamura T et al. (2006) Essential role of Pten in body size determination and pancreatic beta-cell homeostasis *in vivo*. Mol. Cell. Biol 26, 4511–4518 [PubMed: 16738317]
62. Fraenkel M, Ketzinel-Gilad M, Ariav Y, Pappo O, Karaca M, Castel J, Berthault MF, Magnan C, Cerasi E, Kaiser N and Leibowitz G (2008) mTOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. Diabetes 57, 945–957 [PubMed: 18174523]
63. Tee AR, Fingar DC, Manning BD, Kwiatkowski DJ, Cantley LC and Blenis J (2002) Tuberous sclerosis complex-1 and −2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. Proc. Natl. Acad. Sci. U.S.A 99, 13571–13576 [PubMed: 12271141]
64. Thoreen CC, Chantranupong L, Keys HR, Wang T, Gray NS and Sabatini DM (2012) A unifying model for mTORC1-mediated regulation of mRNA translation. Nature 485, 109–113 [PubMed: 22552098]
65. Kim SG, Buel GR and Blenis J (2013) Nutrient regulation of the mTOR complex 1 signaling pathway. Mol. Cells 35, 463–473 [PubMed: 23694989]
66. Mori H, Inoki K, Opland D, Munzberg H, Villanueva EC, Faouzi M, Ikenoue T, Kwiatkowski DJ, Macdougald OA, Myers MG Jr, Guan KL (2009) Critical roles for the TSC-mTOR pathway in beta-cell function. Am. J. Physiol. Endocrinol. Metab 297, E1013–1022 [PubMed: 19690069]

67. Shigeyama Y, Kobayashi T, Kido Y, Hashimoto N, Asahara S, Matsuda T, Takeda A, Inoue T, Shibutani Y, Koyanagi M et al. (2008) Biphasic response of pancreatic beta-cell mass to ablation of tuberous sclerosis complex 2 in mice. Mol. Cell. Biol 28, 2971–2979 [PubMed: 18316403]

68. Rachdi L, Balcazar N, Osorio-Duque F, Elghazi L, Weiss A, Gould A, Chang-Chen KJ, Gambello MJ and Bernal-Mizrachi E (2008) Disruption of Tsc2 in pancreatic beta cells induces beta cell mass expansion and improved glucose tolerance in a TORC1-dependent manner. Proc. Natl. Acad. Sci. U.S.A 105, 9250–9255 [PubMed: 18587048]

69. Mori H and Guan KL (2012) Tissue-specific ablation of Tsc1 in pancreatic beta-cells. Methods Mol. Biol 821, 407–419 [PubMed: 22125081]

70. Blandino-Rosano M, Chen AY, Scheys JO, Alejandro EU, Gould AP, Taranukha T, Elghazi L, Cras-Meneur C and Bernal-Mizrachi E (2012) mTORC1 signaling and regulation of pancreatic beta-cell mass. Cell Cycle 11, 1892–1902 [PubMed: 22544327]

71. Hamada S, Hara K, Hamada T, Yasuda H, Moriyama H, Nakayama R, Nagata M and Yokono K (2009) Upregulation of the mammalian target of rapamycin complex 1 pathway by Ras homolog enriched in brain in pancreatic beta-cells leads to increased beta-cell mass and prevention of hyperglycemia. Diabetes 58, 1321–1332 [PubMed: 19258434]

72. Pende M, Kozma SC, Jaquet M, Oorschot V, Burcelin R, Le Marchand-Brustel Y, Klumperman J, Thorens B and Thomas G (2000) Hypoinsulinaemia, glucose intolerance and diminished beta-cell size in S6K1-deficient mice. Nature 408, 994–997 [PubMed: 11140689]

73. Elghazi L, Balcazar N, Blandino-Rosano M, Cras-Meneur C, Fatrai S, Gould AP, Chi MM, Moley KH and Bernal-Mizrachi E (2010) Decreased IRS signaling impairs beta-cell cycle progression and survival in transgenic mice overexpressing S6K in beta-cells. Diabetes 59, 2390–2399 [PubMed: 20622167]