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Noncanonical Regulation of cAMP-dependent Insulin Secretion and Its Implications in Type 2 Diabetes

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Abstract

Impaired glucose tolerance (IGT) and β-cell dysfunction in insulin resistance associated with obesity lead to type 2 diabetes (T2D). Glucose-stimulated insulin secretion (GSIS) from β-cells occurs via a canonical pathway that involves glucose metabolism, ATP generation, inactivation of K_{ATP} channels, plasma membrane depolarization, and increases in cytosolic concentrations of $[Ca^{2+}]_c$. However, optimal insulin secretion requires amplification of GSIS by increases in cyclic adenosine monophosphate (cAMP) signaling. The cAMP effectors protein kinase A (PKA) and exchange factor activated by cyclic-AMP (Epac) regulate membrane depolarization, gene expression, and trafficking and fusion of insulin granules to the plasma membrane for amplifying GSIS. The widely recognized lipid signaling generated within β-cells by the β-isoform of Ca^{2+}-independent phospholipase A_2 enzyme ($iPLA_2\beta$) participates in cAMP-stimulated insulin secretion (cSIS). Recent work has identified the role of a G-protein coupled receptor (GPCR) activated signaling by the complement 1q like-3 (C1ql3) secreted protein in inhibiting cSIS. In the IGT state, cSIS is attenuated, and the β-cell function is reduced. Interestingly, while β-cell-specific deletion of $iPLA_2\beta$ reduces cAMP-mediated amplification of GSIS, the loss of $iPLA_2\beta$ in macrophages (MØ) confers protection against the development of glucose intolerance associated with diet-induced obesity (DIO). In this article, we discuss canonical (glucose and cAMP) and novel noncanonical ($iPLA_2\beta$ and C1ql3) pathways and how they may affect β-cell (dys)function in the context of impaired glucose intolerance associated with obesity and T2D. In conclusion, we provide a perspective that in IGT states, targeting noncanonical pathways along with canonical pathways could be a more comprehensive approach for restoring β-cell function in T2D.

Introduction

Glucose is the major *in vivo* regulator of insulin secretion from the pancreatic islet β-cells. Elevations in circulating levels of glucose prompt increased transport of glucose into the β-cells, where it enters the glycolytic pathway. Second messengers derived during the

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metabolism of glucose signal through multiple pathways to trigger the exocytosis of insulin from β-cells to affect a return to a euglycemic state. With obesity and/or type 2 diabetes (T2D), there is a progressive defect in β-cell function to the extent that insulin release is insufficient to control blood glucose levels optimally. A primary defect in these individuals is the inability of the β-cells to respond to glucose.

Molecular mechanisms contributing to glucose-stimulated insulin secretion (GSIS) from β-cells have been described in the context of well-characterized canonical pathways. These are initiated by the transport of glucose into the β-cells, followed by the metabolism of glucose, leading to adenosine 5′-triphosphate (ATP) generation, inactivation of the K_{ATP} channels, and increases in $[Ca^{2+}]_c$, triggering insulin exocytosis. It has long been recognized that to achieve optimal insulin secretion, cyclic adenosine monophosphate (cAMP) generation and cAMP-mediated activation of downstream pathways that transduce signals to the plasma membrane and nucleus levels are integral to the amplification of GSIS. As such, cAMP might be regarded as a nexus through which various factors can modulate insulin secretion, *ipso facto*, β-cell function.

Ongoing studies of β-cell function during the healthy and diseased states continue to reveal additional pathways or modulators of GSIS. These may be considered to encompass noncanonical pathways that have important roles in the overall secretory function of β-cells. It has long been recognized that lipid signaling generated within the β-cells through activation of the β-isoform of Ca^{2+}-independent phospholipase A_2 enzyme ($iPLA_2\beta$) participates in GSIS. More recent work has provided evidence for a reciprocal impact of a β-cell secreted protein, complement 1q like-3 (C1ql3), on β-cell function. Intriguingly, both $iPLA_2\beta$ and C1ql3 signaling intersect with the cAMP amplification pathway. In this article, we discuss canonical and novel noncanonical pathways involving $iPLA_2\beta$ and C1ql3 and suggest how they may converge to affect β-cell (dys)function and modulate glucose intolerance in obesity and T2D.

Canonical Mechanism for Insulin Secretion

Biphasic GSIS

In response to elevations in circulating glucose concentrations, pancreatic islet β-cells secrete insulin. Glucose enters the cells via the plasma membrane transporter Glut2 in rodents or Glut1 in humans. It is rapidly metabolized by oxidative glycolysis to increase the ratio of ATP to adenosine diphosphate (ADP). Elevations in the intracellular ATP levels promote the inhibition of ATP-sensitive potassium channels (K_{ATP}), leading to depolarization of the plasma membrane. Consequently, voltage-dependent Ca^{2+} channels (VDCC) open to permit Ca^{2+} influx, facilitating the formation of the soluble *N*-ethylmaleimide-sensitive factor attachment receptor (SNARE) protein complex-dependent fusion of insulin granules to the plasma membrane. This triggering of the exocytotic process releases a short but robust burst of insulin for the first 10 min of glucose stimulation (16, 158, 395). This is referred to as the early phase of the biphasic glucose response. During this early phase, the fusion of insulin granules primarily occurs from the readily releasable pool (RRP) of predocked granules located within 100 to 200nm of the plasma membrane (59, 289, 372). Subsequently, a sustained second phase of insulin secretion persists for several

hours with relatively reduced insulin secretion rates. During this sustained phase, insulin granules from the storage pool present in the cytoplasm distal to the plasma membrane are recruited and undergo plasma membrane fusion (372). These granules, referred to as *newcomers*, undergo fusion mainly via two modes of action: "*short dock*" or "*no dock*." The short-dock newcomer insulin granules traffic to the plasma membrane and undergo docking before fusion, whereas no-dock newcomer insulin granules are "fast-release" and do not require docking before undergoing fusion. In addition to the predocked granules, the fusion of newcomer granules contributes partly to the insulin released in the early phase (238, 251, 311). The burst of insulin released in the early phase is critical for priming the skeletal muscle for sustained, long-term insulin-dependent glucose clearance. During the development of impaired glucose tolerance (IGT), typically associated with insulin resistance due to obesity, a reduction of early-phase insulin secretion occurs. In T2D, insulin secretion from both early and sustained phases is severely reduced. Overall, reduced GSIS is associated with IGT (18, 148, 186, 245, 250, 261, 311, 372).

Triggering and amplifying pathways of GSIS

Glucose metabolism generates signals for triggering and amplifying pathways in insulin secretion (Figure 1). The triggering pathway involves increases in $[Ca^{2+}]_c$, which directly contribute to the exocytosis of insulin granules (151, 153, 341). Multiple factors or mechanisms can contribute to the increases in β-cell $[Ca^{2+}]_c$ (34, 39, 87, 95, 268, 290, 295, 387). However, the best elucidated mechanism for the influx of Ca^{2+} is the opening of the VDCC in response to depolarization of the plasma membrane potential achieved by the closure of K_{ATP} channels. The K_{ATP} channels are complex structures comprising pore-forming Kir6.2 and regulatory sulfonylurea receptor 1 (SUR1) subunits (198, 223). Nutrient signaling effectors such as ATP generated during glycolysis or nonnutrient insulin secretagogues such as sulfonylureas (SUs) bind to the SUR1 or Kir6.2, causing the closure of K_{ATP} channels, which leads to membrane depolarization, increases in Ca^{2+} influx, and triggering of insulin secretion.

While there is ample evidence for the role of K_{ATP} in GSIS, the ability of glucose to amplify insulin secretion was demonstrated using a pharmacological bypass of the K_{ATP} channels when $[Ca^{2+}]_c$ was clamped at an elevated level. This was achieved by treating islets with diazoxide in combination with KCl. Diazoxide binds directly to SUR1 to keep the K_{ATP} channels open, while KCl affects the depolarization of the plasma membrane. In this experimental paradigm, even when K_{ATP} channels were held open by diazoxide, KCl treatment caused plasma membrane depolarization, leading to increased $[Ca^{2+}]_c$ and insulin secretion. Adding glucose in the presence of KCl and diazoxide resulted in higher increases in insulin secretion with minimal or no further increases in $[Ca^{2+}]_c$ compared to the KCl and diazoxide treatment (91, 92, 116). Another study (91, 92, 116) showed that treating islets with high concentrations of SUs (e.g., tolbutamide), which bind to and elicit the closure of K_{ATP} channels, caused the clamping of β-cell $[Ca^{2+}]_c$ at elevated levels, leading to increases in insulin secretion. The addition of glucose caused further increases in insulin secretion without affecting $[Ca^{2+}]_c$ levels. These studies demonstrated the presence of an amplifying pathway in GSIS that is independent of K_{ATP} channels and does not require further increases in $[Ca^{2+}]_c$, suggesting that the amplifying pathway essentially increases

the efficacy of $[Ca^{2+}]_c$ in insulin secretion. Henquin et al. (121) evaluated the physiological significance of the amplifying pathway by assessing insulin secretion in response to glucose where $[Ca^{2+}]_c$ is allowed to fluctuate freely. Under these conditions, a sigmoidal relationship was observed between the [glucose]-dependent curves, where the insulin secretion-response curve was shifted to the right of $[Ca^{2+}]_c$. This implies that signals, in addition to $[Ca^{2+}]_c$, are also generated by glucose that contribute to insulin secretion (114, 121). Complementing these studies, islets from mice with deletion of SUR1 or Kir6.2 (inactivation of K_{ATP} channel) also exhibited plasma membrane depolarization and increases in $[Ca^{2+}]_c$ and insulin secretion (231, 241, 279). Furthermore, plasma membrane depolarization-mediated increases in $[Ca^{2+}]_c$ were observed upon the deletion of K_{ATP} channels, implicating a role of transducers other than the K_{ATP} channels in increasing $[Ca^{2+}]_c$ and insulin secretion. The amplifying pathway contributes approximately 50% to GSIS (118) during the early and sustained phases of insulin secretion. While its physiological importance in mouse and human islets (337) is accepted, the underlying molecular mechanisms are not completely elucidated.

cAMP signaling in stimulus-coupled insulin secretion

In addition to an increase in $[Ca^{2+}]_c$, which is required for triggering insulin secretion, cAMP functions as a key second messenger to amplify GSIS. Increased β-cell production of cAMP facilitates the exocytosis of insulin in both the early and sustained phases of secretion (12, 257, 341) and contributes to whole-body glucose homeostasis (29, 75, 98, 126, 138, 173, 176, 177, 310, 311, 347). The major effects of cAMP in promoting insulin release are attributed to plasma membrane depolarization, $[Ca^{2+}]_c$ signaling, recruitment of insulin granules to the plasma membrane, and activation of the exocytosis machinery (12) (Figure 2).

The Gαs coupled G-protein coupled receptor (GPCR) agonists such as glucagon, glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide-1 (GLP1), pituitary adenylyl cyclase (AC) activating polypeptide (PACAP), and adrenocorticotropic hormone (ACTH) increase GSIS by increasing cAMP via activation of ACs, which convert ATP to cAMP. Increased cAMP signaling accounts for approximately 60% to 70% of total insulin output from β-cells in response to oral glucose stimulation (75, 176). In contrast, reduced cAMP signaling and inhibition of insulin secretion by somatostatin, epinephrine (130), neuropeptide Y (NPY), and EP_3 occur through the activation of Gi-coupled coupled receptors (GPCRs) (65, 259). Relatively less is known about GPCRs that inhibit cAMP production and GSIS. Kimple and Gannon recently assessed the role of cAMP-inhibitory (i.e., G_i-coupled) prostaglandin E_2 (PGE_2)-EP_3 receptor (EP_3) signaling, and they reported that PGE_2 production and secretion, and EP_3 expression are up-regulated in islets isolated from T2D mice and humans (174, 300). Consequentially, GSIS was mitigated, and the maximal potentiating effect of GLP1R ligands on the process was blunted. The EP_3 receptor is among a small group of inhibitory GPCRs whose role in β-cells has been well-characterized (36, 37, 47, 174–176, 243, 293, 297, 298, 300, 352, 382). Additionally, evidence of increased cAMP levels in response to glucose was obtained based on studies where Ca^{2+} was clamped (75) or by using a fluorescence resonance energy transfer (FRET)-based cAMP indicator (172). Moreover, a requirement of cAMP in insulin secretion

was demonstrated using a membrane-permeable antagonist of cAMP, *para*-acetoxybenzyl (pAB) ester prodrug (304). The mechanisms by which exposure of islets to high glucose concentrations promotes increases in cAMP levels and how increases in cAMP signaling via activation of soluble and membrane-bound ACs function in amplifying insulin secretion require further clarification.

The Gαs protein is critical for optimal β-cell function, and the ablation of Gαs in mice leads to impaired β-cell proliferation, reduced insulin gene expression, and glucose intolerance (389). It is known that Gαs activates ACs and potentiates both phases of insulin secretion (267). The ACs are localized in the membrane (AC1–AC9) and cytosol (referred to as *soluble* AC), AC10 (62, 88, 102, 179, 347). Most AC isoforms are expressed in pancreatic islets and insulinoma cells (102, 192), and their function is affected by $[Ca^{2+}]$ (50, 62, 365), providing a link between cAMP and Ca^{2+} signaling. The Ca^{2+}-activated (AC1 (179), AC3 (308), AC6 (192), AC8 (62, 69)) and Ca^{2+}-insensitive AC9 (256) have regulatory functions in rodent mouse β-cells (347). In human β-cells, AC5 was reported to regulate GSIS (124, 192, 397). The soluble AC is activated by HCO_3^- (derived from CO_2 generated during glycolysis) and Ca^{2+} and acts as a potential sensor of ATP generated during glycolysis (128). Its activation has been reported to increase cAMP oscillations and is implicated in increasing insulin secretion in response to high glucose (75). Overall, activated ACs increase cAMP levels, which causes the amplification of insulin secretion. Another class of enzymes, the phosphodiesterases (PDEs), decrease intracellular (cAMP) by hydrolyzing cAMP to 5′ AMP, leading to a reduction in insulin secretion (reviewed in (88, 171, 346)).

Protein kinase A (PKA) is an effector of cAMP

The PKA is a well-characterized serine/threonine kinase and is comprised of two regulatory (RI and RII) and catalytic subunits each. The binding of cAMP to binding sites in the R subunits of PKA leads to conformational changes in the R subunits, causing the release of the catalytic subunits to confer kinase activity. Agonists of PKA amplify GSIS and tolbutamide-stimulated insulin secretion by augmenting the actions of $[Ca^{2+}]_c$ on insulin exocytosis (120). The alpha (α) isoform of the type I R-subunit of PKA is abundantly expressed in mouse and human islets (136, 260, 319). Ablation of RIα from β-cells increased GSIS and glucose tolerance (136, 330), demonstrating its inhibitory function. Consistently, mutations identified in RIα caused increases in insulin release from human β-cells (330), illustrating its relevance in human β-cell function. Moreover, expressing a constitutively active catalytic subunit of PKA in mouse β-cells promotes increases in both phases of GSIS (157). Intriguingly, these genetic alterations of PKA that lead to increases in insulin secretion do not induce hypoglycemia, highlighting the importance of cAMP/PKA signaling and suggesting that it is a viable target for developing therapeutic drugs to improve insulin secretion in obesity and T2D (136).

The PKA-dependent phosphorylation of VDCC (12, 165), K_{ATP} (201), and Kv (191) channels affect stimulus-coupled insulin secretion. Voltage-dependent K^+ currents are modulated by delayed rectifying K^+ (Kv) channels that repolarize the action potential in the plasma membrane (39). The Kv2.1 and Kv2.2 are major channel types in both mouse and human β-cells, and their inactivation increases insulin secretion (143, 200). PKA

promotes the inhibitory effects of cAMP on the Kv channels (191, 206). This prolongs plasma membrane depolarization, increasing $[Ca^{2+}]_c$ and insulin secretion. In addition to Kv channels, PKA has been implicated in inhibiting the K_{ATP} channels in an ADP-dependent manner in response to high glucose (201); the cellular ADP levels are low in β-cells in response to high glucose. Under this condition, PKA binds to the Kir6.2 subunit at serine-372 or SUR1 subunit at serine-1448 to inhibit K_{ATP} channels (25), potentially aiding in plasma membrane depolarization and consequently increasing insulin secretion. PKA-induced phosphorylation of VDCC, primarily of Cav1.3, and the mobilization of internal Ca^{2+} stores by Ca^{2+}-induced Ca^{2+} release (CICR) (74, 162) are also implicated in insulin secretion (204). While increases in PKA activity are proportional to increases in cAMP levels (246), cAMP-elevating agents have no effect in increasing β-cell $[Ca^{2+}]_c$ in the absence of stimulatory concentrations of glucose. These observations suggest that the potentiating effects of cAMP/PKA require triggering levels of $[Ca^{2+}]_c$, which facilitate the PKA-mediated amplification of insulin secretion.

The PKA is also implicated in increasing the sensitivity of $[Ca^{2+}]_c$ for insulin exocytosis by acting more distally to regulate β-cell $[Ca^{2+}]_c$ and by sensitizing the effects of Ca^{2+} on the insulin secretory machinery (325, 369). This is achieved by increasing RRP of insulin granules and the trafficking of insulin granules to the plasma membrane (123). Several proteins have been identified as targets of PKA; however, only a few in the secretory machinery, such as synaptotagmin-7 and snapin, upon phosphorylation, have been found to directly regulate the fusion of insulin granules to the plasma membrane during insulin exocytosis. Synaptotagmin-7 is an insulin granule protein that acts as a Ca^{2+} sensor and functions to accelerate the formation of the SNARE complexes (386). PKA-dependent phosphorylation of snapin (330) increases its interaction with the SNARE complex proteins synaptosomal-associated protein (SNAP25) and vesicle-associated membrane protein 2 (Vamp2), and of synaptotagmin-7 at serine 103 (386) to increase SNARE complex-mediated fusion of insulin granules during insulin exocytosis (330).

Exchange protein activated by cyclic-AMP (Epac2) is an effector of cAMP

The cAMP guanine nucleotide exchange factor (GEF), belonging to the receptor-associated protein (Rap) family of small GTPases (99), is the main Epac isoform that regulates insulin secretion (126, 167, 192, 247, 254). Epac2 contains a regulatory region with two cAMP binding domains and a catalytic region. The binding of cAMP to the regulatory region frees the catalytic region for Epac2 function (281). The Epac2 selective analog 8-pCPT-2′*O*-Me-cAMP was reported to increase the early and sustained phases of insulin secretion from both mouse (163, 167) and human islets (51). Antisense oligonucleotide-mediated knockdown of Epac2 decreased incretin-mediated potentiation of insulin secretion by 50%, attenuating both phases of insulin secretion from mouse islets (167). Though the Epac2 analog does not activate PKA or PKA substrates (CREB, cAMP-response element binding protein, and kemptide), PKA inhibitors blocked the ability of the Epac2 analog to potentiate GSIS, suggesting that PKA has a permissive role in insulin secretion (51). Epac2 has a PKA-independent role in potentiating the effects of cAMP on insulin secretion (78, 283), and mice lacking Epac2 exhibit reduced potentiation of GSIS in response to cAMP (316). Furthermore, Shibasaki et al. showed that the cAMP potentiation of the early phase

insulin secretion was through Epac2 (316). Elevation of cAMP facilitates the localization of Epac2 to the plasma membrane near the insulin granules (11). Moreover, Epac2 clusters are present at the docking site for the insulin granules, facilitating priming and exocytosis (11). Increases in the early phase of insulin secretion are achieved by Epac2-mediated increase in the abundance of RRP (187, 316) and the recruitment of insulin granules from RRP fusion to the plasma membrane (101).

A plausible mechanism suggested for the potentiation of insulin secretion by Epac2 implicates modulation of the fusion of insulin granules to the plasma membrane by the small GTPase Rap1, which Epac2 activates in a cAMP-dependent manner (187). Subsequently, Rap1 activates phospholipase C-epsilon (PLCε) (328), which contains a Rap1-associated domain, allowing activation by cAMP-Epac2-Rap1. The PLCε hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate inositol 1,4,5-trisphosphate (IP_3) and the lipid metabolite diacylglycerol (DAG) (9). As a second messenger, DAG binds and activates protein kinase C (317) and insulin granule priming factor Munc13–1 (26) to facilitate insulin secretion. Consistently, knockout of PLCε disrupts the ability of the Epac2 analog to potentiate GSIS (76), further supporting the role of cAMP-Epac2-Rap1-PLCε in regulating insulin secretion.

Overall, PKCs potentiate GSIS by regulating cortical actin rearrangement and phosphorylation of exocytotic proteins such as synaptotagmin, SNAP25, and Munc18 (key for regulating syntaxin-mediated plasma membrane fusion of insulin granules) (183, 351). Munc13–1, in turn, binds and activates the insulin granule fusion complex assembly to facilitate insulin secretion. Thus, PLCε links cAMP signaling to DAG-mediated potentiation of GSIS via PKC and Munc13–1. Additionally, Rab-interacting molecule 2α (Rim2α) has been implicated in mediating the effects of Epac2 on insulin secretion, as evidenced by an impairment in insulin secretion with Rim2α deletion (392). Rim2α has been reported to interact with an insulin granule-associated Rab3 GTPase (76) to regulate the docking and priming of insulin granules by interacting with Munc13–1 and the SNARE-core complex protein syntaxin to facilitate insulin exocytosis (72, 139). Epac2 interacts with Rim2α in a cAMP-dependent and PKA-independent manner (76), and this interaction is required for the potentiation of incretins on insulin secretion (167). The distinct roles of Rap1-PLCε and Rim2α-Munc13–1 signaling pathways in cAMP-Epac2 regulated potentiation of insulin secretion remain to be elucidated.

K^+-channels as targets of cAMP signaling

Studies by several groups have also noted a dependence of cSIS on K^+-channel activity. The SUs are known to bind to the SUR1 subunit of the K_{ATP} channels, causing membrane depolarization, the influx of Ca^{2+}, increases in $[Ca^{2+}]_c$, and subsequent increases in insulin secretion. SUs such as tolbutamide have been reported to bind and activate Epac2 (122, 394). However, while the interaction between Epac2 and SUs (280, 354) could not be confirmed, the ability of tolbutamide to increase insulin secretion was attenuated in Epac2-null mice (394). These findings support the role of Epac2 in mediating the insulin-promoting effects of SUs via the K_{ATP} channels (145). Epac2 was found to interact with the SUR1 subunit of K_{ATP} channels (254) and functions by activating the Ras-like small G protein Rap

in a cAMP-dependent manner. In β-cells, upon stimulation by SUs, Epac2 activates Rap1 to facilitate its interaction with PLCε. As expected, the ability of Epac2-specific analogs to potentiate GSIS and increase β-cell $[Ca^{2+}]_c$ was found to be disrupted in mice lacking plasma membrane-associated PLCε (76, 200). These outcomes suggest that Rap1-regulated PLCε links Epac2 activation by SUs to Ca^{2+}-dependent exocytosis of insulin (76, 200). In addition to the K_{ATP} channels, activation of Epac2 inhibits voltage-dependent potassium (Kv) channels, thus prolonging the duration of the action potential and causing a delay in membrane repolarization, leading to increases in Ca^{2+} influx and insulin secretion (396). However, the molecular mechanism by which Epac2 modulates the activity of Kv channels to regulate insulin exocytosis remains to be elucidated. Molecular docking stimulation and site-directed mutagenesis analyses have identified that SUs and cAMP cooperatively activate Epac2 by binding to cyclic nucleotide-binding domains (340). Mice lacking Epac2 had a severe reduction in insulin secretion in response to the combined treatment of incretin, GLP1, and SUs (339), suggesting that Epac2 is a critical node that links incretin hormone signaling and SUs in β-cells to increases in insulin secretion, thus connecting the triggering and amplifying pathways to insulin exocytosis.

cAMP signaling in β-cell adaptation

The development of insulin resistance typically associated with obesity triggers a compensatory β-cell adaptive response, which involves altered insulin secretory capacity and increased β-cell mass. Alterations in these attributes evoke responses in the β-cells that culminate in the increased net output of insulin into the plasma to maintain euglycemia during an insulin-resistant state. When β-cells are unable to compensate completely (i.e., fail) to meet the increased demand for insulin due to genetics and/or environmental factors in the face of insulin resistance, glucose intolerance increases and leads to the development of an IGT state, which initially results in mild hyperglycemia and then to elevated hyperglycemia leading to T2D development.

The compensatory β-cell response to insulin resistance ensures that sufficient insulin is released from the pancreas into the plasma to maintain euglycemia. Moreover, complete compensation involves increased plasma insulin levels with normal glycemia, whereas, in partial compensation, plasma insulin levels are elevated with mild hyperglycemia. In these compensating phases, the increases in plasma insulin levels are not particularly associated with increases in the secretory capacity of β-cells but are attributed to increases in the β-cell mass (291). Details on the role of β-cell mass during compensation are thoroughly discussed elsewhere (52, 141, 203, 234, 375).

Multiple studies have shown that early β-cell dysfunction occurs with the onset of insulin resistance in the pathogenesis of T2D. As insulin resistance continues to increase, progressive β-cell dysfunction contributes to hyperglycemia in T2D (81, 86, 147, 233, 331, 364, 379). This has been shown in populations such as Japanese Americans and Asian Americans (331, 364), who are generally not obese, and in Pima Indians (379), where insulin secretion defects occur early in T2D progression. Furthermore, groups with increased risk of T2D, such as normoglycemic first-degree relatives of individuals with T2D (54, 263), women with polycystic ovary syndrome (73), or with a history of gestational

diabetes (373, 388) were shown to have early onset of β-cell dysfunction. In 1987, Nesher et al. showed that individuals with T2D have reduced pancreatic responsiveness without differences in peripheral insulin sensitivity compared to obese nondiabetic individuals (242). DeFronzo's group assessed β-cell function in relation to peripheral insulin sensitivity in lean, obese normal glucose tolerant, obese IGT, and obese T2D individuals. They reported that obese individuals with normal glucose tolerance have significantly reduced β-cell function compared to healthy individuals (4, 5, 60, 85). They further demonstrated that IGT reduced β-cell function by nearly 70%. These studies show that by the time a diagnosis of T2D is made, patients have significantly reduced β-cell function. Prentki and Khan corroborated these observations in studies performed using high-fat diet-induced obese (DIO) mice (135, 261). Their work showed that the DIO mice exhibited hyperinsulinemia, impaired glucose tolerance, with reduced *ex vivo* islets insulin secretion in response to glucose compared to mice on the standard chow diet (135, 261). However, another study reported increases in GSIS in islets isolated from DIO mice compared to controls (96). It is essential to determine the causes for the reductions in early and progressive β-cell functions with IGT during the compensation phase to delineate the mechanisms contributing to T2D. This will facilitate the development of more targeted and effective therapeutics for T2D.

GLP1 incretin contributes to β-cell adaptation by increasing cAMP signaling to facilitate β-cell proliferation and differentiation while decreasing apoptosis (149, 166). Studies in rodents reveal that activation of the cAMP downstream effector PKA causes translocation of the transcription factor CREB and transducer of regulated CREB activity-2 (TORC2) into the nucleus and induction of genes such as *MafA1, Nkx6.1*, *Pdx1*, recognized to impact β-cell mass and function (8, 21, 30, 366, 368). Exogenous treatment of GLP1 or GLP1 agonists in mice increases insulin secretion and glucose clearance (315), and genetic ablation of GLP1R or pharmacological blockage of GLP1R attenuates insulin secretion and glucose clearance (292, 305). The GLP1R signaling is known to be dysfunctional in T2D (53, 70, 180, 282, 353). Moreover, the sensitivity of GLP1 for β-cells is reduced in obese and T2D, compared to healthy individuals (20), and is attributed to reduced cAMP signaling. The β-cell cAMP levels are reduced in hyperglycemia and T2D, and islets from individuals with IGT or T2D have reduced early and sustained phases of GSIS and a blunted response to GLP1 (282, 353). Increasing cAMP signaling improves overall β-cell function in obesity and T2D and enhances the ability of GLP1 to improve β-cell dysfunction in T2D (348). Also, injecting GLP1 increased β-cell mass and insulin secretion in DIO mice treated with streptozotocin (135). These studies suggest that GLP1/cAMP signaling has beneficial effects in improving β-cell function and β-cell mass. However, the underlying molecular mechanisms that reduce GLP1/cAMP signaling in T2D require clarification.

The reduction in the early phase of insulin secretion indicates β-cell dysfunction is observed in insulin-resistant prediabetic individuals wherein the cellular insulin content is still not altered (78). Treatment with GLP1 receptor agonists can completely restore this secretory defect in prediabetes, implicating that GLP1 potentially functions by improving glycolysis-generated ATP-mediated closure of the K_{ATP} channels (78). This is supported by the findings that GLP1 cannot potentiate insulin secretion in mice lacking SUR1 and Kir6.2 subunits of the K_{ATP} channels (230, 239, 319). Conversely, neonatal diabetes patients harboring a gain-of-function mutation in the SUR1 have attenuated GSIS due to overactive

K_{ATP} channels (38), whereas treatment with GLP1R agonists potentiated GSIS in these patients. The Epac2 and PKA are effectors of GLP1/cAMP signaling that inhibit K_{ATP} channels; Epac2 by enhancing the ability of ATP to inhibit the Kir6.2 (164), and PKA by reducing the stimulatory actions of Mg^{2+}-ADP at SUR1 (201). Thus, it is possible that GLP1/cAMP, via its effectors Epac2 and PKA, directly inhibits K_{ATP} channels. However, the molecular mechanism by which an increase in GLP1R signaling modulates K_{ATP} channel activity is not completely elucidated. In addition to the K_{ATP} channels, GLP1 signaling also inhibits the delayed rectifier voltage-dependent K^+ current (Kv) (217), prolonging the duration of the action potential, and thereby increasing the influx of Ca^{2+} by VDCC and enhancing insulin secretion.

The role of Epac2 in regulating insulin secretion from β-cells has been demonstrated in insulin resistance and obesity (127). Ablation of Epac2 in DIO mice was reported to increase body weight and reduce glucose intolerance and insulin secretion compared to mice on the control diet (137, 329). Furthermore, the glucose-lowering effects of SUs and GLP1 agonist liraglutide treatment were attenuated in *Epac2*$^{-/-}$ DIO mice. This suggests a role for Epac2 in potentiating insulin secretion in response to the combination treatment of SU and liraglutide in T2D (339). In addition, it was found that the disruption of PKA inhibitor B (PKIB) gene (a potent inhibitor of PKA catalytic activity) improved glucose sensitivity and GSIS in DIO mice, suggesting that PKA potentiates insulin secretion (30). These studies show that cAMP/Epac2 and cAMP/PKA are beneficial in potentiating insulin secretion in obesity and T2D. However, the mechanisms by which Epac2 and PKA mediate the effects of GLP1/cAMP signaling on the RRP, priming of insulin granules, Ca^{2+} sensitivity, and insulin exocytosis, and how these attributes are altered in obesity and T2D remain to be elucidated.

Noncanonical Mechanisms for cSIS

Contribution of lipid signaling to insulin secretion

It is well-recognized that lipids, in particular eicosanoids and sphingolipids, participate in inflammatory processes. Here, we discuss their identified roles in β-cell secretory function and how modulation of their signaling can impact GSIS, in the context of obesity and T2D.

Fatty acids

GSIS is potentiated by nonesterified fatty acids (NEFAs), with the potency correlating directly with chain length and desaturation of the fatty acid (220, 252, 265, 333). The NEFAs can promote insulin secretion at basal glucose concentrations (129) and are particularly critical for insulin secretion in healthy nonobese individuals following prolonged fasting (67). During periods of short starvation, unsaturated fatty acids can stimulate, whereas saturated short/medium chain fatty acids decrease insulin secretion (332). It has been suggested that this may be related to the modulation of intercellular signaling that influences higher oxygen consumption rate (48), greater activation of FFAR1/GPR40 signaling (48), or increased triglyceride esterification (77). Consistently, GSIS is enhanced by diets enriched in monounsaturated fatty acids (MUFAs) or PUFAs and diminished by diets enriched in saturated fatty acids (262). Studies in the BRIN BD11 insulinoma cell line suggest that arachidonic acid (AA) stimulates β-cell proliferation and insulin secretion and

that these effects are mitigated by hyperglycemia or the saturated fatty acid palmitate, as in T2D (66).

In addition to the ω-6 AA (C20:4 double bonds), other polyunsaturated fatty acids (PUFAs) hydrolyzed from the *sn*-2 position of membrane glycerophospholipids include the long-chain ω-3 polyunsaturated eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6). Through islet lipid enrichment studies, EPA and DHA have been recognized to provide signaling to improve β-cell secretion under T2D, obesity, or insulin resistance states. In an early study, EPA enrichment was found to prevent lipotoxicity-induced activation of the uncoupling protein-2 (154), which can recover ATP production and preserve insulin secretion (168). Analogously, a diet enriched with both EPA and DHA reduced palmitate-mediated decreases in GSIS and apoptosis by reducing palmitate-induced increases in β-cell reactive oxygen species (207). Concomitantly, a high-fat diet (HFD) enriched in EPA mitigated insulin resistance in a DIO mouse model (205). In an elegant study, supplementing the diet of BTBR *Leptin*$^{ob/ob}$ mice with EPA was reported to decrease the production of PGE_2 from AA and increase the production of the EPA metabolite PGE_3, which is 10-fold less potent in reducing GSIS when compared to PGE_2 (244, 284). Moreover, EPA also decreased the expression of the PGE_2 receptor, EP_3. Fewer studies have been performed with DHA alone. Nevertheless, DHA supplementation has been reported to reduce insulin resistance in obese humans (2). Moreover, EPA and DHA index correlated positively with increased insulin sensitivity in obese men (10). Interestingly, overweight obese and diabetic women, but not men, had lower plasma levels of EPA and DHA (3), implying a sex-difference association of these ω-3 fatty acids with T2D. The protective effects of these ω-3 fatty acids in obesity and T2D were reasoned to be related to reductions in AA levels that occur with EPA and/or DHA supplementation. Furthermore, EPA and DHA potentially function to alter membrane structure, fluidity, and signal transduction, which are beneficial for β-cell function (13, 156). Also, EPA and DHA are thought to signal through the GPCR (GPR)120 receptor (249) to induce GLP-1 secretion from enteroendocrine L-cells to promote insulin secretion (27). In islets, GPR120 expression has been identified in β-cells, and lipid agonists of GPR120 were found to promote insulin secretion through inhibition of somatostatin secretion, and GPR120 signaling was found to be impaired in the *db/db* mouse (71). An ω-3 metabolite of EPA, 5-hydroxyicosapentaenoic acid (5-HEPE), has been reported to enhance GSIS and cAMP generation (181) by signaling through the GPR119 receptor, which is predominantly expressed in β-cells (253).

Eicosanoids

Metabolism of AA in β-cells generates oxidized bioactive lipids (Figure 3) that have been implicated in insulin secretion. Forty years ago, studies identified an inhibitory effect of PGE_2 on GSIS (229, 287, 306). This was later attributed to PGE_2 signaling via the EP_3 receptor to inhibit c-Jun N-terminal kinase (JNK1) activation of AKT serine/threonine kinase 1 (AKT) phosphorylation leading to downstream dephosphorylation of the transcription factor forkhead box protein O1 (FOXO1), facilitating its entry into the nucleus to dysregulate insulin synthesis and GSIS (226, 227). Alternatively, reduced GSIS has also been associated with EP_3 receptor signalling-mediated decreases in cAMP production (47, 174), and inhibiting EP_3 receptor signaling improves insulin secretion from islets of

T2D donors (174). Reports along these lines have led to further exploration of targeting EP3 receptors to counter β-cell dysfunction and the progression of T2D (243). Similarly, PGD_2 has been reported to reduce GSIS by signaling through the PGD_2 receptor GPR44/DP2, highly expressed in human β-cells (202), to inhibit cAMP production (1). In T2D, GPR44/DP2 expression is increased in islets (115), and while *in vitro* inhibition of this receptor increased GSIS from human islets, short-term *in vivo* inhibition was without affect (326). Additionally, cytokines contribute to β-cell dysfunction in T2D (68, 327, 378). In particular, interleukin-1β (IL-1β) is elevated in islets from T2D donors and induces cyclooxygenase 2 (COX2), leading to increased production of PGE_2 and EP_3 receptor expression, with an overall effect of amplifying PGE_2-EP_3 signaling in the β-cells (56, 255, 350) and reducing GSIS. Consistently intervening with IL-1β receptor signaling improves GSIS (188, 219). Further, PGE_2 generated through the elevated COX2 expression in human islets from T2D donors decreases the expression of genes involved in β-cell function, such as *Pdx1*, *Nkx6.1*, and *MafA1* (371). This raises the possibility of dysregulated metabolism of AA to PGE_2 in T2D islets. Further, PGE_1, which is derived from dihomo-γ-linolenic acid (DGLA) and signals through EP_2 receptor, has been reported to decrease *in vitro* and *in vivo* GSIS (229, 285). A potential mechanism for this is the PGE_1-mediated activation of the G-protein Gz to inhibit β-cell endocytosis, which is an integral component of the exocytosis-endocytosis process that needs to be maintained in equilibrium to preserve β-cell volume for optimal β-cell function (400). In contrast to the above-discussed PGs, prostacyclin (prostaglandin I_2, PGI_2) through PGI_2 receptor (IP)-GPCR signaling induces adenyl cyclase to increase the production of cAMP, which directly activates Epac2 to induce GSIS (105). The potential of PGI_2 analogs in mitigating glucose intolerance and insulin resistance associated with T2D has also been identified (296). Collectively, these studies suggest that several different PGs may serve as therapeutic targets to improve β-cell function in T2D.

HETEs

Other metabolites of AA, such as hydroxyeicosatetraenoic acids (HETE), have also been shown to have profound effects on GSIS. These include 12-HETE and 20-HETE generated by lipoxygenases (LOX) and cytochromes P450 (CYP4A & CYP4F), respectively. Islets from T2D donors are reported to have increased expression of 12-LOX (140). Consistently, the deletion of 12-LOX in a rodent model of T2D is associated with reductions in 12-HETE, preservation of GSIS (345), and inhibition of insulin resistance associated with DIO (248, 307). Similarly, increases in 20-HETE appear to decrease GSIS, and rescue of GSIS is observed with the inhibition of 20-HETE-induced decrease in Glut2 (393). Moreover, the production of epoxyeicosatrienoic acids (EETs) (209), which promote GSIS (83), by CYP2C & CYP2J, also modulates the effects of 20-HETE on GSIS. In contrast to these studies, 20-HETE has been suggested to provide a positive feedback regulation of GSIS by signaling through the G_q/G_{11}-coupled free fatty acid receptor 1 (FFAR1) expressed highly in β-cells (142, 185, 286, 309) to facilitate insulin exocytosis. Interestingly, though the basal levels of 20-HETE in islets from multiple rodent models of T2D and human T2D donors were increased, under conditions of GSIS, the levels of 20-HETE were reported to be decreased, and the addition of selective FFAR1 agonists failed to rescue GSIS in the T2D islets (356). This suggested impairment in the positive regulatory loop on GSIS mediated by

20-HETE in T2D. Human islet FFRA1 mRNA levels were consistently found to correlate positively with the insulinogenic index (349).

EETs

The CYP2-catalyzed metabolism of AA leads to the generation of EETs, which are rapidly metabolized to dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH). Among the EETs, 5,6-EET has been reported to induce insulin secretion (83). However, all isomers of EETs in the plasma of humans correlated positively with insulin sensitivity (90). In a model of K_{ATP}-independent insulin secretion, imidazoline-induced GSIS was reported to occur through AA-derived EET generation (314). Further, because of their rapid degradation, the potential beneficial effects of EETs have mostly been gleaned from examining the effects of inhibiting or reducing the expression of sEH. Luo et al. were the first to demonstrate an improvement of *in vivo* insulin secretion and a reduction in blood glucose levels of streptozotocin diabetic mice with inhibition or deletion of sEH, and an increase in GSIS with sEH inhibition (209). Similar manipulation of sEH in a DIO model also reduced plasma glucose levels and mitigated insulin resistance development (210). In this regard, the expression of CYP2 isoforms was decreased, sEH expression increased with obesity in the Zucker rat model (399), and the knockout of CYP2C44 decreased glucose tolerance and insulin sensitivity (90). Consistently, CYP2J gene therapy resulted in increases in EET levels and reversal of insulin resistance in T2D rodent models (*db/db* and fructose-treated mice) (390). Further, deletion of sEH in *db/db* mice markedly reduced blood glucose levels (131). The effects of EETs in ameliorating T2D are likely related to the prevention of decreases in insulin receptor signaling and phosphorylation of AMP-activated protein kinases (AMPKs) in a variety of peripheral tissues (390). The expression of sEH has been found to increase in islets from mice and macaque maintained on HFD and from T2D donors (182). In the same study, sEH inhibition, genetic reduction, and EET treatment were demonstrated to potentiate GSIS and reduce HFD-induced β-cell death. At the β-cell level, the positive impact of sEH inhibition on GSIS appears to be due to the potentiation of K_{ATP}-independent amplification of insulin secretion involving cAMP signaling (117). Consistently, sEH inhibition or genetic reduction increased glucose-stimulated ATP and cAMP levels in the islets (182). Given these observations, modulating sEH activity is under consideration as therapy for many disorders, including obesity and diabetes (107).

Sphingolipids (SLs)

Another major class of lipids implicated in modulating GSIS and T2D is the SLs (6, 336). Among them, ceramides induce insulin resistance (32, 338) and decrease insulin gene transcription (103) and are reported to be elevated in T2D (6, 108). In contrast, decreasing ceramide synthesis promotes insulin sensitivity (125, 398) and β-cell survival (193, 195). Moreover, elevations in dihydroceramides have been reported in the plasma of subjects that eventually developed T2D (380). Intriguingly, inhibiting *de novo* production of hypothalamic ceramides in the obese Zucker T2D model reduced glucose intolerance and enhanced GSIS (45). In contrast, the ceramide metabolite sphingosine-1-phosphate (S1P), which has the opposite effects of ceramides (190, 318), promotes GSIS by activating sphingosine kinase 2 (SK2) GPCR (46), the predominant SKR expressed in β-cells (225).

Other ceramide-derived SLs have also been suggested to affect GSIS positively or negatively (35).

Phospholipases A_2-derived lipids and β-cell function

Phospholipases A_2 (PLA_2s)—The family of phospholipases A_2 (PLA_2s) catalyzes the hydrolysis of the *sn*-2 substituent from the glycerol backbone of membrane glycerophospholipids to yield a free fatty acid and a lysophospholipid (96). The major constituents of the PLA_2 family are (s)ecretory, (c)ytosolic, and Ca^{2+}-(i)ndependent PLA_2s, with the $iPLA_2$s being the most recent family of PLA_2s described and characterized (41, 64). Ca^{2+} at mM and μM concentrations are essential for the activity of $sPLA_2$s and the membrane association of $cPLA_2$, respectively. In contrast, the $iPLA_2$s mobilize and manifest activity in the absence of Ca^{2+} (270). Among the $iPLA_2$s, the cytosolic $iPLA_2$, designated Group VIA $iPLA_2$ or $iPLA_2$β, was discovered in 1997 (22, 213, 344) and was soon followed by the description of the membrane-associated $iPLA_2$γ (Group VIB $iPLA_2$) in 2002 (221). Other $iPLA_2$s ($iPLA_2$δ, $iPLA_2$ε, $iPLA_2$ζ, and $iPLA_2$η) (42, 146, 301, 367) have since been described but remain to be characterized in detail. Several members of the $sPLA_2$ family have been demonstrated to negatively (group X (322) and V (321)) or positively (IB (276)) influence GSIS, whereas $cPLA_2$ overexpression can promote insulin exocytosis (155), but sustained $cPLA_2$ activation reduces β-cell function and GSIS (152, 232).

$iPLA_2$β and GSIS—Given recent studies concerning mechanisms that promote β-cell decompensation during the development of obesity and T2D, this article focuses on the very first functional role ascribed to $iPLA_2$β, relating to its involvement in insulin secretion. Before its formal description in 1997, work done by the Turk and Gross groups identified a phospholipase A_2 activity in islet β-cells, but not in non-β-cells, that was manifested in the absence of Ca^{2+} and was stimulatable by ATP (100, 273), leading to its initial designation as ASCI-PLA_2 (ATP-stimulatable Ca^{2+}-independent phospholipase A_2) (357). Subsequently, its predominant expression in the β-cells of the islets was demonstrated at the mRNA (213) and protein (194) levels. Cloning of $iPLA_2$β from hamster, mouse, and rat identified protein homologs that are 85 kDa (752 amino acids) (22, 213, 344) with a serine lipase consensus sequence (GTSGT), preceded by eight N-terminal ankyrin repeats (213, 344). In human lymphocyte lines and in testis, $iPLA_2$β was described as containing a 54-amino acid insert interrupting the eighth ankyrin repeat (189), and analyses in human pancreatic islets identified cDNA species that encoded two distinct 85 kDa (VIA-1) and 88 kDa (VIA-2) human $iPLA_2$β isoforms (215). Subsequent characterization of $iPLA_2$β by several groups identified other features in the protein that included: GXGXXG nucleotide-binding motif (214, 221), N-terminal caspase-3 cleavage site (DVTD) (19), putative bipartite nuclear localization sequence (KREFGEHTKMTDVKKPK) (214), and C-terminal 1–9-14 calmodulin-binding motif (IRKGQGNKVKKLSI) and a calmodulin-binding peptide (AWSEMVGIQYFR) (146, 214, 359). Studies in numerous laboratories over the past three decades have identified $iPLA_2$β as a ubiquitous enzyme that has roles in phospholipid remodeling, cell proliferation, apoptosis, and signaling.

Earlier works revealed that fuel secretagogue-induced hydrolysis of β-cell membrane phospholipids promotes accumulations of AA and its metabolites in β-cells (28, 362).

The islets are particularly enriched in AA-containing glycerophospholipids, with 31% residing in glycerophosphoethanolamine (GPE), 53% in glycerophosphocholine, 10% in glycerophosphoinositol, and 3% in glycerophosphoerine (271, 272). The fraction of AA in islet GPE is greater than that in liver, heart, or brain (275) and nearly half of this is contained in plasmenylethanolamine species, as in the brain (275). Further, islet subcellular organelles (mixed membranes, secretory granules, plasma membranes, endoplasmic reticulum) are enriched in AA-containing plasmenylethanolamine molecular species (275), and this pool is the major source of AAs that are hydrolyzed during GSIS (271) and subsequent accumulations in AA correlated with temporal increases in GSIS (273, 274, 278).

Studies by the Turk group revealed that AA at concentrations that accumulate within the β-cell with high glucose stimulation promotes increases in $[Ca^{2+}]_c$ levels (228, 383, 384). Subsequent collaborative efforts with the Phillipson group led to delineation of a molecular mechanism whereby the AA inactivates the β-cell-delayed rectifier potassium channel, Kv2.1, causing a prolongation of glucose-induced action potentials and elevation in $[Ca^{2+}]_c$. *These observations suggest that arachidonic acid also plays a key second messenger role in GSIS* (23, 144).

Prior to the 1990s, the hydrolysis of membrane phospholipids in β-cells was understood to occur via phospholipases that are expressed in β-cells and activated by increases in $[Ca^{2+}]_c$. However, if the hydrolysis of AA induced by glucose were dependent on the Ca^{2+} influx, it would not align temporally with the pathway through which it affects Ca^{2+} influx. A solution to this conundrum was provided by studies demonstrating that glucose-induced release of AA occurred, in part, in the absence of Ca^{2+} or in the presence of Ca^{2+}-channel blockers (358, 383), suggesting the expression of a Ca^{2+}-independent PLA_2 activity. In fact, in the early 1990s, the Gross group reported expression of a myocardial ASCI-PLA_2 (110–113). Subsequently, analogous studies not only identified a similar $iPLA_2$ in β-cells but determined that its activation led to AA accumulation in β-cells and that this correlated with GSIS (100, 273). This $iPLA_2$ was subsequently designated $iPLA_2\beta$, based on the presence of the GXSXG lipase consensus motif and a GXGXXG nucleotide-binding motif that was sequentially first identified in the potato enzyme patatin (14).

The recognition of an $iPLA_2\beta$ activity in the islets prompted a detailed characterization of its role in GSIS, especially in light of the recognition that T2D is characterized by a select defect in GSIS (266). Studies in insulinoma cells and islets (rodent and human) utilizing multiple approaches to modify $iPLA_2\beta$ activity or expression strongly supported the following: (i) GSIS correlates with the $iPLA_2\beta$-dependent accumulation of AA in the β-cells and the release of PGE_2 from β-cells (268, 273, 274, 278), (ii) $iPLA_2\beta$ promotes glucose, but not AA-induced increase in $[Ca_i^{2+}]$ (273) and (iii) $iPLA_2\beta$ activation reduces depolarization-induced Kv2.1 currents, thus promoting Ca^{2+} flux and amplifying GSIS (23, 144). These observations brought to light a positive impact of $iPLA_2\beta$ on promoting insulin secretion from β-cells.

These observations suggest that dysfunction of $iPLA_2\beta$ in β-cells is critical to the development of β-cell decompensation associated with T2D. Indeed, nonglucose secretagogues, but not glucose, have been reported to increase PLA_2 activity and insulin

secretion from islets isolated from mice fed a HFD. This raises the possibility that PLA_2 activation is a mechanism that participates in β-cell compensation associated with insulin resistance (324). In support of this possibility, a recent study demonstrated that mice with a conditional knockout in β-cell $iPLA_2β$ have elevated fasting glucose levels and exhibit glucose intolerance that is exacerbated when maintained on a HFD (360). Deficiency in $iPLA_2β$ was also associated with mitigating obesity in a variety of models (49, 63), reductions in plasma glucose and insulin levels, and improvement in glucose tolerance (63).

Role of complement1q-like 3 (C1ql3) in insulin secretion—Secreted proteins are critical metabolic regulators that play significant roles in cell-cell communication between different cell types. These proteins relay the metabolic status of the origin cell to impart metabolic changes in the target cells in an autocrine, paracrine, or endocrine manner. The roles of islet endocrine hormones such as glucagon, insulin, somatostatin (SST), pancreatic polypeptide (PPY), and ghrelin secreted by alpha (α), beta (β), delta (δ), PP, and epsilon (ε) cells, respectively, have been well-characterized in whole-body glucose homeostasis. Additionally, significant crosstalk occurs within islets between distinct islet cells and a few notable autocrine and paracrine regulators have been identified, such as SST, urocortin-3, islet amyloid polypeptide (IAPP), and glucagon. The SST secreted from δ-cells act on α- and β-cells to inhibit glucagon and insulin secretion, respectively (40, 79, 134). A late β-cell maturity marker, urocortin-3, secreted from β-cells, decreases SST secretion from δ-cells (132). Moreover, glucagon has an intra-islet role in increasing insulin secretion from β-cells. Islet autocrine and paracrine regulators have been previously reviewed (44, 84, 119, 134, 288, 355).

Eleven percent of the human and mouse genome transcripts encode for secreted proteins, and approximately 3000 secreted proteins have been annotated, but the function for most of them remains undescribed (363). To this end, Koltes et al. used an unbiased approach of the weighted gene expression network analysis to identify secreted protein regulators of islet function (184). Using lean and obese islet transcriptomics data, they identified that islets express 850 transcripts encoded for secreted proteins whose expression significantly changes with obesity. This suggested that several islet-derived secreted proteins potentially manifest roles in response to obesity. Islets by mass are only 1% of the total pancreas weight. So, it is conceivable that several of the islet-derived secreted proteins are involved in crosstalk between distinct islet cells in an autocrine and/or paracrine manner in obesity. They further identified 44 hub genes with high connectivity attributes encoding secreted proteins to affect islet function in obesity. Of those, the complement 1q like 3 (C1ql3) secreted protein was reported as a top hub gene, illustrating the utility of unbiased network analysis in identifying secreted protein regulators affecting islet function in obesity. The complement 1q (C1q)/tumor necrosis factor (Tnf)-related proteins (CTRP) are secreted proteins (e.g., adiponectin) that are evolutionarily conserved from zebrafish to humans (385). They have been implicated in lipid and carbohydrate metabolism, immunity, inflammation, and synapse homeostasis (33, 94, 312, 323). C1ql3, also called CTRP13, is a soluble secreted protein whose primary structure resembles proteins encoded by highly homologous genes: C1ql-1, -2, and -4. It is expressed in adipose tissue and the brain of lean mice. Obesity due to a HFD or homozygosity for the $Leptin^{Ob}$ mutation was reported to increase the expression of

C1ql3 in the brain and islets (184), whereas caloric restriction decreases its expression (43). Serum C1ql3 levels are increased in *Leptin*^{Ob} mice (43). Wei et al. have reported that C1ql3 regulates glucose metabolism (374), and epidemiological studies have shown an association between serum C1ql3 levels and T2D and metabolic disorders in humans (7, 80, 82, 313).

C1ql3 is abundantly expressed in islets, and its expression is increased in islets from *db/db*, DIO, and *Leptin*^{Ob} (>30-fold) mice (104). Localization of C1ql3 is in insulin-positive β-cells, but not in α- or δ-cells, identifying β-cells as the source of the secreted C1ql3 protein. The molecular mechanism of obesity-induced transcriptional regulation of C1ql3 and how C1ql3 is secreted from β-cells is unknown. A recent report by Gupta et al. (104) demonstrated that C1ql3 inhibits high glucose (16.7 mM)-stimulated insulin secretion without affecting insulin secretion in response to low (2.8 mM) or sub-maximal (11.1 mM) glucose from mouse islets. Remarkably, C1ql3 almost completely blocked insulin secretion in response to stimulation with exendin-4 (a stable analog of GLP1) and cAMP from mouse and human islets. In addition, C1ql3 also decreased cAMP levels in response to high glucose. Such an inhibitory impact of C1ql3 on insulin secretion was confirmed using mouse and human C1ql3 recombinant proteins, C1ql3-conditioned media, knockdown approaches in clonal β-cells, and mouse and human islets. Since high glucose treatment is known to increase cAMP levels in β-cells by activating soluble AC (124, 192, 397), the inhibitory effect of C1ql3 on insulin secretion in response to high glucose could be due to the attenuation of cAMP signaling. Remaining to be elucidated are the molecular mechanisms and the physiological significance of β-cell C1ql3 in regulating islet function to affect whole-body glucose homeostasis in lean vs. obesity states (Figure 4).

The brain-specific angiogenesis inhibitor 3 (BAI3) has been identified as a receptor for C1ql3 (224). The BAI3 is a member of the BAI subfamily of adhesion GPCRs. These proteins are involved in synaptogenesis, angiogenesis, and tumor suppression (57, 235, 320). Structurally, BAI3 is comprised of an extracellular N-terminal CUB domain, four thrombospondin type 1 repeats, a hormonebinding domain, the GPCR auto-proteolysis-inducing domain (GAIN) with an auto-proteolysis site (GPS), the characteristic 7-transmembrane repeat of a GPCR, an intracellular α-helical RKR motif, and PDZ domain-binding motif (57). BAI3 is expressed primarily in the brain and has been implicated in psychiatric disorders such as schizophrenia, bipolar disorder, and addiction (169, 197). It is also expressed in islets and muscles, and mutations in BAI3 have been linked to T2D in human GWAS studies (109, 150). The BAI3 receptor is coupled to Gi and has a role in early-onset venous thromboembolism risk (15), stimulation of testosterone secretion (342), and myoblast fusion (106). Further, BAI3 signaling is required in the synaptic organization, acquisition of social transmission of food preference (370), and mediation of cell-cell adhesion (334). In β-cells, siRNA-mediated knockdown of BAI3 increased insulin secretion from INS1(832/13) cells and is implicated in mediating the inhibitory effects of C1ql3 on insulin secretion (104). These studies suggest a role for this poorly characterized BAI3 signaling in insulin secretion affecting β-cell function. The molecular mechanism by which C1ql3/BAI3 regulates islet function remains to be elucidated.

Perspective: Potential Interplay Between iPLA$_2$β and C1ql3 During T2D Development

Nearly 35 million people in the USA have T2D, and obesity is a major risk factor for T2D (196, 303). A key feature of T2D development is that during the initial phase of obesity-induced metabolic stress, β-cells compensate for increasing insulin secretion to achieve glucose homeostasis. However, chronic obesity manifests insulin resistance, prompting further attempts of β-cell compensation until the β-cells cannot overcome the metabolic demands and begin to fail (133). The concept of β-cell compensation progressing to β-cell decompensation is entrenched in the T2D field. However, mechanisms that contribute to this eventuality are still not completely understood.

There is strong evidence in the literature that defects in insulin granule exocytosis machinery, metabolism, and electrical activity contribute to β-cell dysfunction in IGT associated with obesity and T2D (81, 89). The early phase insulin secretion loss is the initial event during the development of β-cell dysfunction in IGT (81). This is attributed primarily to defects in insulin exocytosis, as cellular insulin content is not significantly altered during this state. Treatment with GLP1 receptor agonists that increase cAMP signaling can restore early phase insulin secretion deficits (315), highlighting the role of downstream cAMP effectors Epac2 and PKA in improving glucose responsivity of the β-cells to secrete insulin. The overall mechanism of how PKA and Epac2 mediate GLP1/cAMP effects on improving insulin secretion in IGT is not completely understood. It is possible that upon activation, PKA and Epac2 increase the ability of glucose to inactivate K_{ATP} and Kv2.1 channels, delaying membrane repolarization, thus increasing the duration of the action potential and enhancing the rise in $[Ca_c]^{2+}$ (58, 191, 199, 218, 335, 391). These events promote the fusion of insulin granules to the plasma membrane for insulin exocytosis. Epac2 binds to and inhibits K_{ATP} channels (145, 254), whereas PKA phosphorylates K_{ATP} (25) and Kv (191, 206) channels. In addition to regulating plasma membrane electrical activity, Epac2 and PKA can directly affect the secretory machinery (325, 369) of the insulin granules by facilitating the RRP pool, docking, priming, and fusion of insulin granules to the plasma membrane (386). Furthermore, cAMP/PKA regulates β-cell gene expression through CREB to increase insulin secretion (8, 21, 30, 366, 368). The beneficial effects of GLP1/cAMP signaling in improving β-cell function are well established. However, the precise mechanism by which PKA and Epac2 function in improving β-cell dysfunction in IGT remain to be determined (Figure 5).

When the clinical diagnosis of T2D is made, the β-cell function is already reduced by 70% (4, 5, 60, 85). Moreover, normal and impaired glucose-tolerant obese individuals also have significantly decreased β-cell function (4, 5, 60, 85). The mechanisms that cause this reduction in β-cell function are not yet completely understood. Stable GLP1 analogs (e.g., exenatide, liraglutide, semaglutide) are currently wellaccepted T2D therapeutics with many advantages over older β-cell secretagogues that function in a glucose-independent manner (e.g., SUs, glinides) (264). These GLP1 agonists have been the most successful approaches in T2D treatment, and their effect in improving β-cell function is via the GPCR-mediated activation of cAMP signaling. Even though stable GLP1 analogs function in a

physiologically relevant manner, they remain ineffective or insufficiently effective in 20% to 40% of T2D individuals in improving β-cell function (55, 161, 178). Thus, a complete understanding of how β-cell cAMP signaling is regulated in the healthy, obese, and T2D states is essential for developing interventions for improving β-cell function in IGT for treating individuals with T2D. The canonical approach involves elucidating the downstream molecular mechanism by which cAMP regulates β-cell function. An additional approach involves identifying and characterizing signaling pathways that either directly activates, antagonize, or synergize with the cAMP signaling to modulate β-cell function. Elucidating these cell-signaling pathways that modulate cAMP signaling would be key to improving our understanding of β-cell adaption that can also be targeted to increase the efficacy of GLP1 analogs that are used for the treatment of T2D. In this regard, we have identified *C1ql3* and *iPLA*$_2$β as manifesting opposing effects on the cAMP pathway in the β-cells.

C1ql3 negatively impacts insulin secretion

C1ql3 is secreted from islet β-cells and has its maximal inhibitory effect on insulin secretion in response to stimulation by exendin-4 (GLP1 agonist) and cAMP (104, 184), implicating it as an autocrine regulator of insulin secretion. Moreover, C1ql3 was found to not affect insulin secretion in response to submaximal or basal glucose concentrations, mitochondrial metabolites (isocitrate, α-ketoglutarate, malate, and glutamate), amino acids (leucine, glutamine, alanine, arginine), or fatty acids (monoacylglycerols, DAGs, palmitate) (104, 184). The expression of C1ql3 and BAI3 is increased by greater than 30-fold and 4-fold, respectively, in islets obtained from euglycemic obese mice, during conditions when β-cells are undergoing functional adaption to obesity or IGT associated with insulin resistance. Thus, it is plausible that the activation of C1ql3/BAI3 signaling in β-cells during obesity contributes to regulating cAMP signaling mediated β-cell adaptation during IGT/T2D state. Elucidating the precise molecular mechanism of how C1ql3/BAI3 regulates cAMP-signaling in β-cells within a healthy pancreas, as well as under pathogenic conditions such as obesity and T2D, will elucidate whether C1ql3 contributes to β-cell dysfunction associated with IGT in obesity and T2D. It is broadly accepted that β-cell mass is increased to adapt to obesity-associated insulin resistance (52, 141, 203, 234, 375). However, the relationship between proliferation and functional maturity of β-cells is poorly understood. Several studies have suggested that proliferating β-cells are functionally immature (31, 222, 269, 302). Thus, it is possible that C1ql3 signaling also has a role in reducing the responsivity of β-cells to glucose/cAMP for optimal insulin secretion in the proliferating β-cell population.

iPLA$_2$β positively impacts insulin secretion

The ubiquitous Ca^{2+}-independent PLA$_2$ (iPLA$_2$β) (22, 146, 221, 344) hydrolyzes the *sn*-2 substituent of membrane glycerophospholipids to yield a free fatty acid and a 2-lysophospholipid (237, 361). The iPLA$_2$β participates in cellular lipid metabolism, signaling, energy homeostasis (170, 237, 381), and *amplification of cSIS* (212, 216, 271, 274, 277, 278). Supporting a role for iPLA$_2$β in insulin secretion are the findings that islets from global iPLA$_2$β-null mice exhibit impaired GSIS (23, 24) in the presence of forskolin, which activates AC to generate cAMP. These mice exhibit normal glucose tolerance in the unstressed state (24) but develop more severe glucose intolerance while exhibiting better insulin sensitivity than wild-type littermates when subjected to DIO (24).

This discordance of the effects of DIO on insulin secretion and sensitivity in the global iPLA$_2$β-null mice suggests that iPLA$_2$β plays distinct roles in the molecular mechanisms underlying insulin secretion and insulin action and in the impact of DIO on these processes. Arachidonic acid is a major *sn*-2 substituent in β-cell membranes, and its iPLA$_2$β-mediated hydrolysis correlates with stimulated insulin secretion (24, 100, 212, 216, 271, 274, 277, 278). Mechanistically, arachidonic acid has been reported to inactivate the inward rectifier Kv2.1 channel to prolong β-cell membrane polarization and enhance Ca^{2+} influx (23, 144). This is recapitulated in β-cells overexpressing iPLA$_2$β and mitigated in iPLA$_2$β-null β-cells (23, 144) treated with glucose and carbachol, which signals through acetylcholine receptors to increase cAMP generation in the β-cells.

Linking C1ql3 and cell-specific iPLA$_2$β to cAMP signaling

The ability of cAMP signaling to improve β-cell function is reduced in IGT (obese and T2D) states (282, 353). It has been reported that glucose tolerance and cSIS in mice with select deficiency in β-cell-iPLA$_2$β (iPLA$_2$β$^{\beta KO}$) are impaired (360) and are exacerbated in DIO mice. Conversely, cSIS insulin secretion and glucose tolerance improvement occur in mice overexpressing iPLA$_2$β (iPLA$_2$β$^{\beta TG}$) in β-cells. These observations support a role for β-cell-iPLA$_2$β in maintaining glucose tolerance and improving β-cell function. Understudied but critical contributors to islet inflammation in T2D are the macrophages (MØ), and MØ and precursor monocytes express iPLA$_2$β (97, 236, 258, 343). Activation of iPLA$_2$β favors polarization of MØ to an inflammatory M1 phenotype (17, 240), which triggers events that contribute to diet-induced insulin resistance in diabetes and obesity (159, 160, 208, 294, 376, 377). We find that mice with select iPLA$_2$β deficiency in MØ (iPLA$_2$β^{MØKO}) have improved β-cell function, glucose tolerance, and insulin sensitivity (360). Thus, increased MØ-iPLA$_2$β signaling contributes to the detrimental effects of MØ on β-cell dysfunction in IGT/T2D, countering the beneficial effects of β-cell iPLA$_2$β signaling in improving cSIS. The expression of C1ql3 and BAI3 is increased in islets during IGT, implicating that enhanced C1ql3/BAI3 signaling in β-cells could potentially be exacerbating the reduction of cAMP signaling, thereby contributing to β-cell dysfunction in IGT/T2D. This could be achieved by C1ql3/BAI3 signaling to decrease the ability of iPLA$_2$β to increase cSIS (Figure 6).

GSIS is reduced from pancreatic β-cells, in the context of impaired glucose tolerance (IGT) and T2D (18, 148, 250, 261, 311, 372). Furthermore, amplification of GSIS in response to the incretins is also blunted. Decades of work established that cAMP is essential for promoting insulin secretion and maintaining whole-body glucose homeostasis (176, 299, 310, 347). β-cell cAMP levels and signaling are reduced in islets from individuals with IGT or T2D (282, 353). The Gs-coupled receptor signaling, including for GLP1, in β-cells, is very well characterized, however, little is known about factors that function to regulate cAMP signaling. Targeting C1ql3 and iPLA$_2$β that function reciprocally to increase GLP1/cAMP signaling is an innovative strategy to improve β-cell function in obesity/T2D. Excitingly, it could also provide a solution for improving the effectiveness of GLP1 drugs that are used for T2D treatment. An intriguing path is to resolve the previously unrecognized crosstalk between two well-established pathways involving iPLA$_2$β and GLP1 signaling, and how C1ql3 modulates their roles to affect β-cell (dys)function. We posit that the study of

a link between iPLA$_2$β and C1ql3 could elucidate the initial signaling events that contribute to β-cell dysfunction in the IGT state associated with obesity *before* the clinical diagnosis of T2D (61, 93, 211, 233). Table 1 lists the abbreviations used throughout the article.

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Didactic Synopsis

Major teaching points

- β-Cell dysfunction is observed during impaired glucose tolerance states associated with obesity and type 2 diabetes (T2D).
- Insulin secretion from β-cells occurs through well-understood canonical and less-understood noncanonical pathways.
- The canonical pathways include: (i) triggering and amplifying pathways that regulate glucose-stimulated insulin secretion (GSIS) and (ii) the amplification of GSIS by activating cAMP signaling via PKA/Epac proteins.
- A requisite for optimal stimulus-coupled insulin secretion is the activation of cAMP signaling in β-cells.
- Noncanonical pathways include signaling by C1ql3 secreted protein and iPLA$_2$β-derived lipids generated within the β-cells.
- C1ql3 and iPLA$_2$β signaling intersect at the cAMP level to produce opposing effects on insulin secretion.
- It is speculated that the dysregulation of C1ql3 and iPLA$_2$β proteins contributes to the β-cell dysfunction associated with obesity and T2D.
- Detailed studies of these noncanonical pathways will improve our understanding of β-cell secretory function/capacity and offer new therapeutic avenues to counter impaired β-cell function in obesity and T2D.

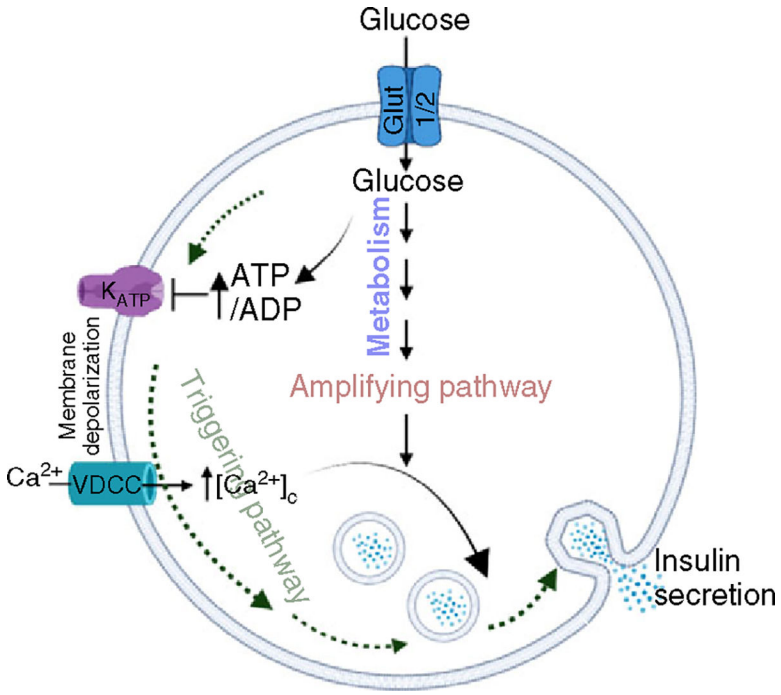

Figure 1. Triggering and amplifying pathways of glucose in increasing insulin secretion (GSIS) from β-cells.

Glucose enters the β-cells via the Glut2 in rodents and Glut1 in humans transporters and undergoes metabolism by the glycolytic pathway. The increase in the ATP/ADP ratio causes inhibition of the K_{ATP} channels. This causes the depolarization of the plasma membrane, causing the influx of Ca^{2+} through VDCC. The subsequent increase in $[Ca^{2+}]_c$ facilitates the fusion of insulin granules to the plasma membrane. This step is called the triggering pathway. The metabolism of glucose leads to generation of metabolites or second messengers that amplify the ability of $[Ca^{2+}]_c$ to increase insulin secretion. This is called the amplifying pathway of GSIS.

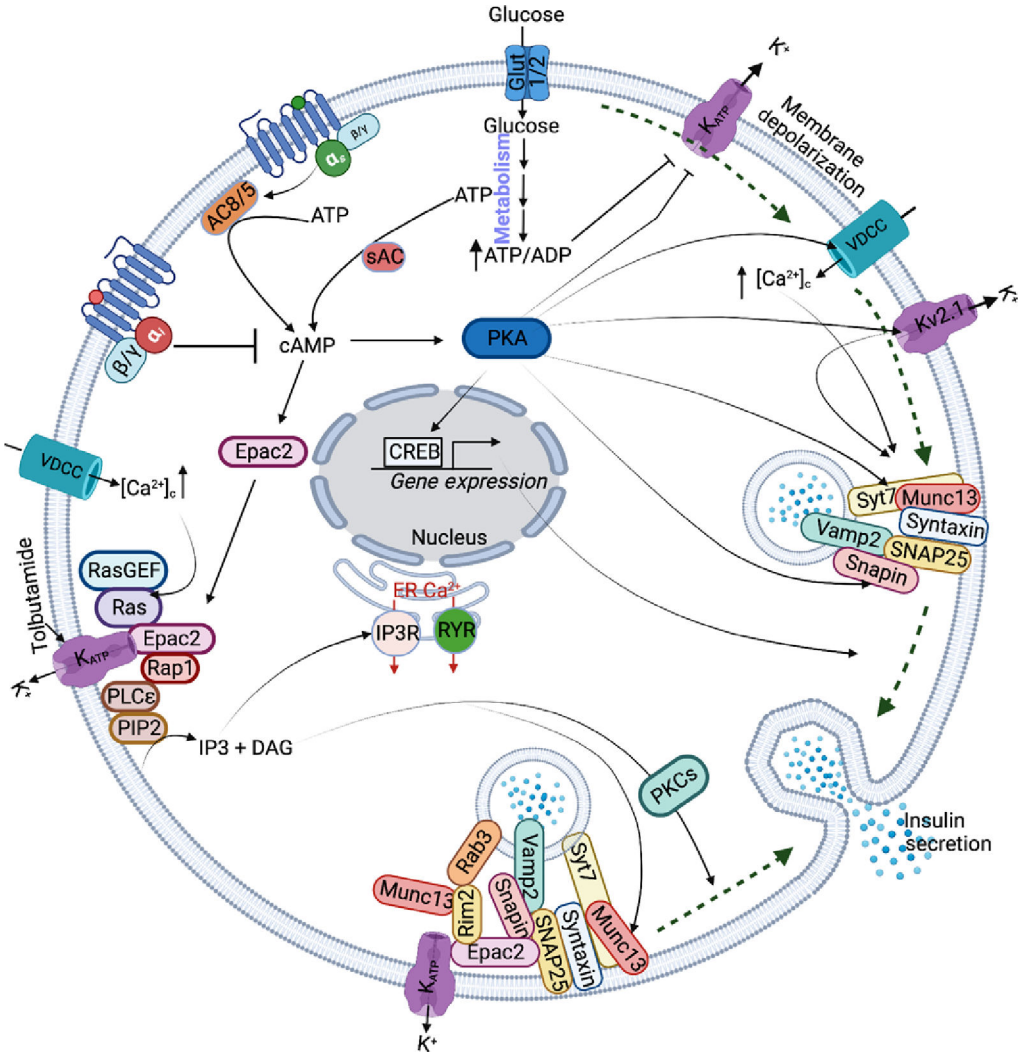

Figure 2. Cyclic AMP signaling amplifies GSIS in β-cells.

The green dotted line shows the triggering pathway of glucose in increasing insulin secretion. The activated Gs-coupled GPCR signaling increases cAMP levels thereby activating its downstream effectors Epac2 and PKA. Subsequently, PKA increases insulin secretion by modulating the function of VDCC, Kv2.1, K_{ATP}, Snapin, and Syt7, and nuclear translocation and activation of CREB. Epac2 binds K_{ATP} channels, causing activation of IP3 and DAG. The IP3 increases Ca^{2+} release from the ER, and DAG binds and activates the Munc13–1 priming factor and PKC to increase insulin secretion by facilitating the fusion of insulin granules to the plasma membrane.

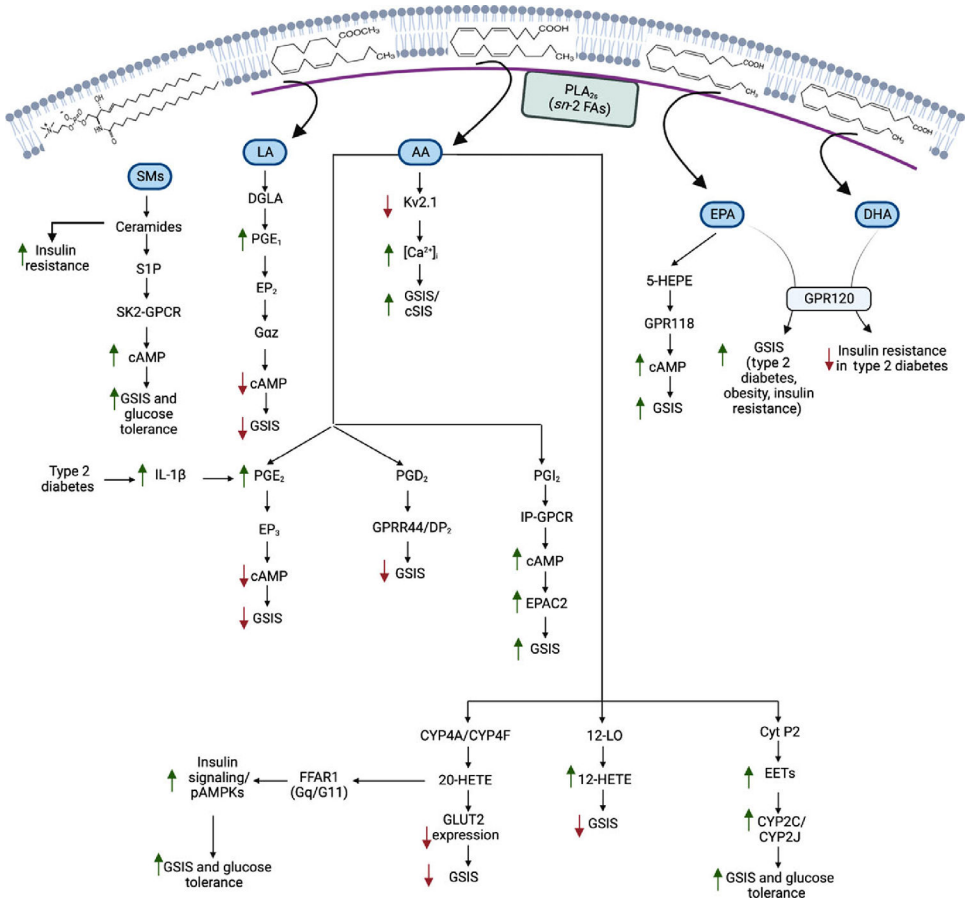

Figure 3. Contribution of β-cell-derived lipids to insulin secretion.

Elevations in circulating glucose concentrations induce phospholipases A_2 (PLA_2s)-catalyzed hydrolysis of the *sn*-2 fatty acid substituent from β-cell membranes. The released fatty acids can then be metabolized by oxidases to generate bioactive lipid mediators (e.g., PGs, prostaglandins; HETEs, hydroxyeicosatetraenoic acids; and EETs, epoxyeicosatrienoic acids). Further, membrane-associated sphingomyelins can be hydrolyzed by sphingomyelinases to ceramides, which can be converted to sphingosine-1-phosphate (S1P). These lipids via intracrine, autocrine, paracrine, and endocrine mechanisms are recognized modulators of insulin secretion.

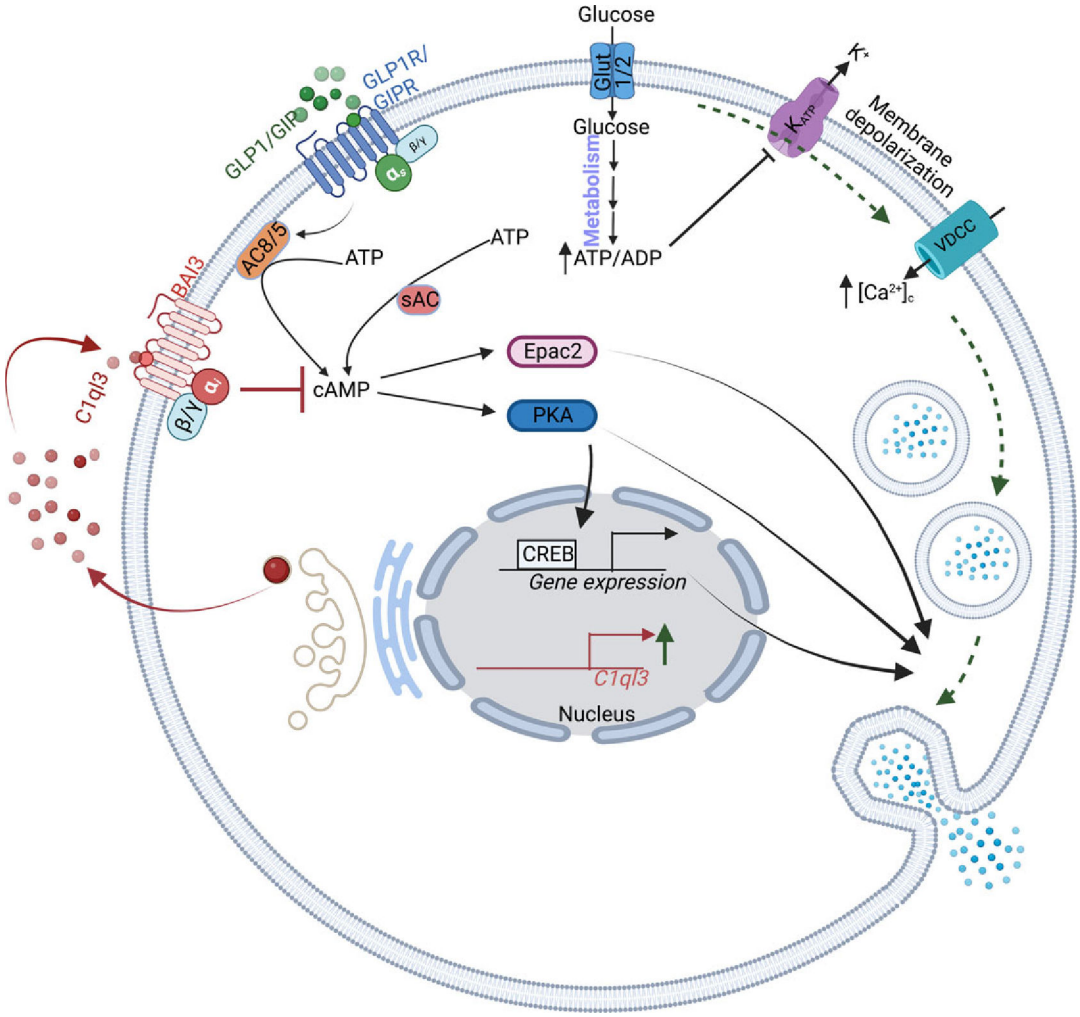

Figure 4. C1ql3 regulates cAMP signaling and amplifies GSIS in β-cells.

Upon secretion from β-cells, C1ql3 signals in an autocrine manner by binding to its receptor BAI3 to regulate insulin secretion by inhibiting cAMP signaling.

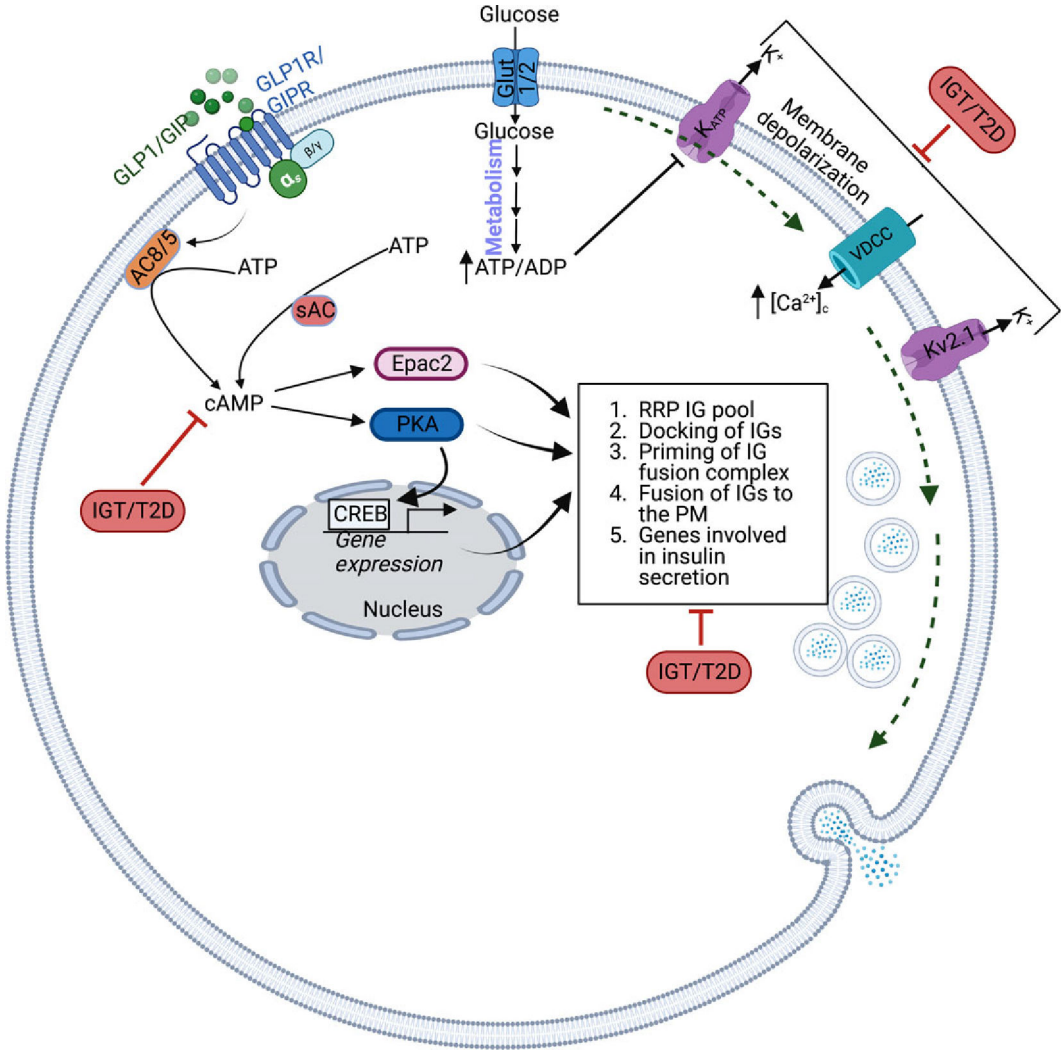

Figure 5. IGT and T2D can affect multiple aspects of the cAMP signaling to decrease insulin secretion.

The IGT/T2D states can potentially reduce cAMP levels, size of the RRP insulin granule (IG) pool, docking of the IGs to the plasma membrane, priming of the IGs to the plasma membrane, the fusion of the IGs to the plasma membrane, and PKA-CREB mediated β-cell gene expression. Additionally, IGT/TD can also decrease the ability of glucose to cause plasma membrane depolarization-regulated insulin secretion.

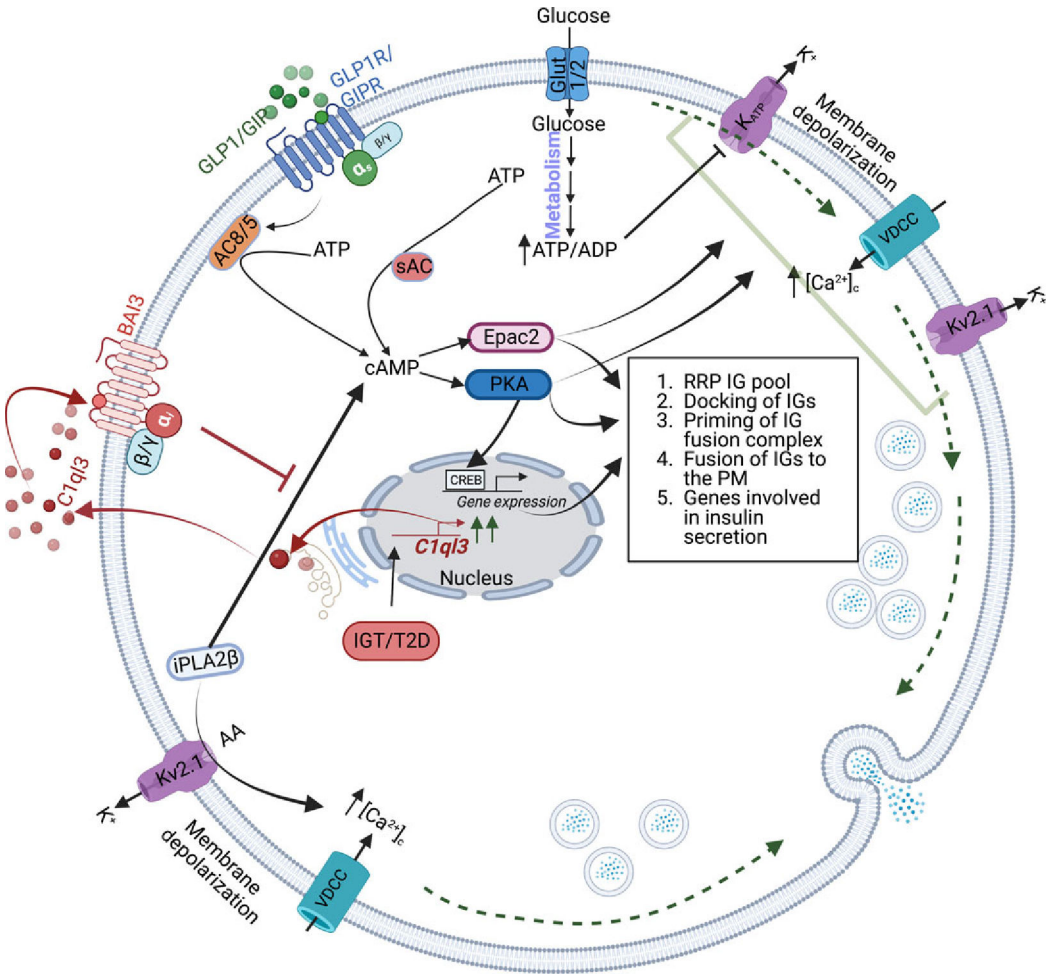

Figure 6. Proposed role of the noncanonical signaling pathways affecting the β-cell secretory function during IGT and T2D.

During IGT/T2D, mRNA abundance and the secretion of C1ql3 are increased from the β-cells. The C1ql3 binds to and activates its receptor BAI3 to decrease cAMP signaling, affecting the RRP of IGs, docking of IGs, the priming of IGs, fusion of IGs, and PKA-CREB-regulated expression of genes. Another signaling event mediated by iPLA$_2$β causes an increase in cSIS. The interplay between C1ql3 and iPLA$_2$β in IGT/TD could be important in modulating cAMP signaling, affecting insulin secretion from β-cells during IGT/T2D.

Table 1

Abbreviation List

AA	arachidonic acid
AC	adenylate cyclase
ADP	adenosine diphosphate
AKT	Ak strain transforming serine/threonine kinase 1
AMK	AMP-activated protein kinases
ATP	adenosine 5′-triphosphate
BAI3	brain-specific angiogenesis inhibitor 3
Ca^{2+}	calcium ion
$[Ca^{2+}]_c$	cytosolic Ca^{2+} concentration
cAMP	cyclic adenosine monophosphate
CICR	Ca^{2+}-induced calcium release
C1ql3	complement 1q-like-3
COX	cyclooxygenase
$cPLA_2$	cytosolic phospholipase A_2
cSIS	cAMP-stimulated insulin secretion
CTRP13	C1q/TNF-related protein 13
CUB	complement C1r/C1s, Uegf, Bmp1
CREB	cAMP-response element binding protein
CYP	cytochrome *P450*
DAG	diacylglyceride
DGLA	dihomo-γ-linolenic acid
DHA	docosahexaenoic acid
DHET	dihydroxyeicosatrienoic acids
DIO	diet-induced obesity
DP2	prostaglandin D_2 receptor
EET	epoxyeicosatrienoic acids
EP	PGE_2 receptor
EPA	eicosapentaenoic acid
Epac	exchange protein activated by cyclic-AMP
FFAR1	free fatty acid receptor 1
FOXO1	forkhead box protein O1
FRET	fluorescence resonance energy transfer
GAIN	G-protein-coupled receptor (GPCR) autoproteolysis-inducing domain
GEF	guanine nucleotide exchange factor
GRP	G protein-coupled receptor
Gs	Gs protein
Gi	Gi protein
Gα	Gs alpha subunit
GIP	glucose-dependent insulinotropic polypeptide
GLP1	glucagon-like peptide-1

GPCR	G-protein coupled receptor
GPE	glycerophosphatidylethanolamine
GPR120	G-protein coupled receptor 120
GPR119	G-protein coupled receptor 119
GPR44	G-protein coupled receptor 44
GPS	glycerophosphatidylserine
GSIS	glucose-stimulated insulin secretion
GWAS	genome-wide association studies
HEPE	hydroxyeicosapentaenoic acid
HETE	hydroxyeicosatetraenoic acid
HFD	high-fat diet
IAPP	islet amyloid polypeptide
IG	insulin granule
IGT	impaired glucose tolerance
IP3	inositol trisphosphate
$iPLA_2$	Ca^{2+}-independent phospholipase A_2
$iPLA_2\beta$	β-isoform of Ca^{2+}-independent phospholipase A_2
$iPLA_2\beta^{\beta KO}$	select-deficiency of $iPLA_2\beta$ in β-cells
$iPLA_2\beta^{\beta TG}$	select overexpression of $iPLA_2\beta$ in β-cells
JNK1	c-Jun N-terminal kinase
K^+	potassium ion
K_{ATP}	potassium-sensitive ATP-channel
Kv2.1	delayed rectifier K^+-channel
LOX	lipo-oxygenase
MØ	macrophages
M1	inflammatory MØ phenotype
MAFA1	MAF BZIP Transcription Factor A
MUFA	mono-unsaturated fatty acid
Munc	mammalian uncoordinated-18
NEFA	nonesterified fatty acid
NKX6.2	NK6 Homeobox 2
PDE	phosphodiesterase
PDXl	pancreatic and duodenal homeobox l
PDZ	modular protein-protein interacting domain
PKA	protein kinase A
PGE_2	prostaglandin E_2
PGI_2	prostaglandin I_2
PKC	protein kinase C
PLA_2	phospholipase A_2
PLCε	phospholipase C-epsilon
PUFAs	polyunsaturated fatty acids
P450	cytochrome *P450*

PGD_2	prostaglandin D_2
PUFA	polyunsaturated fatty acid
Rab	Ras superfamily of small G proteins
Rap	receptor-associated protein
RIα	R-subunit
RIM	Rab-interacting molecules
RRP	readily releasable pool
sEH	soluble epoxide hydrolase
siRNA	small interfering RNA
SL	sphingolipid
SMase	sphingomyelinase
SNAP	synaptosomal-associated protein
SNARE	soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor
S1P	sphingosine-1-phosphate
$sPLA_2$	secretory phospholipase A_2
SU	sulfonylurea
SUR1	sulfonylurea receptor 1
T2D	type 2 diabetes
TF	transcription factor
Tnf	tumor necrosis factor
TORC2	transducer of regulated CREB activity-2
Vamp2	vesicle-associated membrane protein 2
VDCC	voltage-dependent Ca^{2+}-channels