

Lipotoxicity and β Cell Maintenance in Obesity and Type 2 Diabetes

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Obesity and diabetes are often associated with lipotoxic conditions in multiple tissues. The insulin-producing β cells are susceptible to elevated lipid levels and the ensuing lipotoxicity. The preservation of β cell mass and function is one of the main goals of diabetes management under these metabolically stressful conditions. However, the adverse effects from the adaptive signaling pathways that β cells use to counteract lipotoxic stress have secondary negative effects in their own right. Antilipotoxic signaling cascades in β cells can contribute to their eventual failure. Such dual roles are seen for many other biological adaptive processes as well.

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Lipotoxicity refers the detrimental effects of lipid metabolites on nonadipose tissues, such as liver, skeletal muscle, heart, kidney, and pancreatic β cells [1]. It is a pathologic process seen in many metabolic disorders, most notably obesity and type 2 diabetes [2]. Excessive caloric intake or defective lipid metabolism leads to an oversupply of triglycerides, cholesterol, and free fatty acids (FFAs), which eventually exceed the storage capacity of adipose tissue and are enriched in plasma. This process leads systemic pressure on many tissues and cells to increase their lipid uptake. Interstitial or intracellular accumulation of lipids and their toxic metabolic products, such ceramides, diacylglycerol, and fatty acyl-CoA, can impair tissue function and cellular metabolism [3]. The resultant complications include hepatic steatosis, cardiovascular disease, renal failure, and peripheral insulin resistance [4].

Pancreatic β cells are professional secretory cells releasing insulin, an essential hormone regulating glucose and lipid metabolism. With minimal regenerative capacity during adulthood, β cells are susceptible to cellular stresses caused by reactive oxidative species (ROS), protein misfolding, and lipotoxicity [5]. The failure of β cells paves the path to end-stage type 2 diabetes. Here, we discuss recent insights obtained from studies on the impact of lipotoxicity on β cell function and survival, the cellular processes and molecular signaling that β cells use to counteract lipotoxic effects, and the adverse consequences of inducing these counterregulatory mechanisms. These insights derived from studying the antilipotoxic responses in β cells may provide the basis for more effective clinical approaches geared toward β cell preservation in obesity and type 2 diabetes.

Abbreviations: AdipoR, adiponectin receptor; AMPK, AMP-activated protein kinase; DIO, diet-induced obese; eIF4E, eukaryotic translation initiation factor 4E; ER, endoplasmic reticulum; FFA, free fatty acid; GLP1R, glucagon-like peptide-1 receptor; GPR, G-protein-coupled receptor; GSIS, glucose-stimulated insulin secretion; IR, insulin receptor; IRS, insulin receptor substrate; LRP1, lipoprotein receptor-related protein 1; mTORC, mammalian target of rapamycin complex; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxidative species; UPR, unfolded protein response.

1. β Cell Deterioration in Lipotoxic Environments

Hyperlipidemia is a key pathological feature shared by obesity, diabetes mellitus, and metabolic syndromes, and it imposes chronic insults on β cells via generation of intracellular cytotoxic metabolites and activation of detrimental signaling pathways, eventually leading to β cell dysfunction and death [6]. The critical role of environmental lipids in β cell pathology was first proven in rodent models. For instance, Unger [7] showed that in Zucker diabetic fatty rats, a genetic model of obesity and type 2 diabetes, mitigation of plasma FFAs can prevent β cell dysfunction. Interestingly, even in insulinopenic diabetes, high circulating lipids contribute to further β cell loss, driving a vicious positive feedback toward a collapse of systemic lipid homeostasis [8]. Studies in humans have generated mixed results. A 3-year follow-up study in Europe found associations between plasma nonesterified fatty acid levels and insulin resistance but not glucose-stimulated insulin secretion (GSIS) in β cells. In contrast, a recently reported 6-year follow-up study in Canada showed a strong negative correlation between serum nonesterified fatty acids and β cell function, as indicated by the insulinogenic index over homeostatic model assessment of insulin resistance (IR) and the insulin secretion-sensitivity index-2 [9]. More studies will be needed to explain the discrepancies and generalize the conclusions.

As for mechanistic studies, Jacqueminet *et al.* [10] investigated the effects of long-term saturated FFA exposure (*i.e.*, palmitate over the course of days and weeks) on the transcription of the insulin genes. With isolated rat islets in culture, they discovered that excessive FFA suppresses insulin expression at high glucose levels but not with basal glucose. This effect is also observed *in vivo* in rat models [11] and can be explained by the high glucose-driven FFA esterification into triglycerides [12]. Other groups reported impairments in proinsulin synthesis and insulin secretion induced by high FFAs and high glucose [13]. The synergistic effects of glucose and saturated FFAs also apply to β cell apoptosis, as seen in rat and human β cell cultures [14], which can be reversed by monounsaturated fats [15]. The underlying reasons for the increased rate of apoptosis are attributed at least in part to increased β -oxidative activity [12, 14] that is associated with higher levels of DNA breaks [16].

Multiple additional factors and signaling pathways have been reported to mediate the lipotoxic effects in β cells. Ceramides are a class of sphingolipids that can induce apoptosis in a variety of tissues [17]. In human β cells exposed to FFAs, this effect is mediated by caspase activation [18]. Serine palmitoyltransferase catalyzes a key step of FFA conversion into ceramides [19]. Inhibitors of ceramide synthases can block the palmitate-induced β cell death [15]. The ceramidase activity of adiponectin receptors protects β cells against lipotoxic apoptosis [20]. Kelpel *et al.* [21] also linked ceramides to the transcriptional suppression of insulin in FFA-treated β cells.

Accumulation of ROS can result in oxidative stress and irreversible β cell injury [22]. Considering the low antioxidant capacity of human β cells, they are highly susceptible to the ROS generated by increased mitochondrial activity under excess nutrient supply [23]. Long-term FFA exposure inhibits the transcription of KIF12, a microtubule motor protein in β cells with potent antioxidative capacity. KIF12 promotes the function of peroxisomes by stabilizing the newly synthesized transcription factor Sp1, which in turn induces the expression of Hsc70 [24]. ROS accumulation can also result from the upregulation of the proinflammatory cytokine IL-1 β -induced divalent metal transporter 1, which triggers increased intracellular iron deposition [25]. In diabetic mouse islets, the cytokines IL-23, IL-24, and IL-33 function as pro-oxidants, and IL-22 has antioxidant capabilities [26]. A recent study has identified the redox adaptor enzyme p66SHC as a link between saturated FFA and oxidative stress in β cells [27]. Oxidative stress can activate the nuclear factor κ B pathway, leading to increased inflammation [28]. In line with that, the inhibition of the proinflammatory kinase IKK β ameliorates FFA-induced β cell dysfunction in mice and rats [29].

Saturated FFAs can induce islet inflammation and β cell dysfunction via the TLR4-MyD88 pathway in β cells [30]. Chemokines and cytokines secreted from β cells lead to the recruitment of M1 macrophages and resulting inflammatory damage. A recent report

identified IL-1R signaling as another culprit for impairments in β cell GSIS and proliferation upon inflammation [31].

Endoplasmic reticulum (ER) stress is also closely associated with β cell failure in diabetes, because of the heavy secretory load that β cells have to carry with proper processing of large amounts of proinsulin [32, 33]. As the major organelle for protein folding and post-translational modifications, the ER is under stress when the unfolded or misfolded protein load exceeds its capacity. In an effort to adapt to these unfavorable conditions, the unfolded protein response (UPR) signaling pathways are activated to reduce protein synthesis, increase ER-associated protein degradation, and promote the expression of protein chaperones [34]. However, if the ER stress is prolonged and beyond the adaptive capacity of the UPR, downstream proapoptotic signaling cascades are activated, leading to a paradoxical upregulation of protein synthesis, depletion of ATP, oxidative stress, and cell death [35]. ER stress in human β cells can be induced by amyloid aggregates [36] or under other conditions characteristic of type 2 diabetes [37]. UPR signaling molecules, such as eIF-2 α phosphorylation, ATF4, CHOP, BiP, ATF6, and spliced XBP-1, are induced in β cells by FFA exposure [38, 39]. Thioredoxin-interacting protein was suggested to link ER stress to inflammation and β cell death [40], and its upregulation was detected in islets from diabetic patients [41]. Upstream of ER stress, saturated FFAs can overload ER by disrupting protein trafficking from ER to Golgi [42], an effect that can be ameliorated by high-density lipoproteins [43]. The loss of sphingomyelin seen under these conditions may disrupt the lipid rafts of ER membrane, thereby reducing the efficacy of vesicular trafficking [44].

In summary, lipotoxicity, usually combined with glucotoxicity in diabetes [6], damages the insulin secretory function and survival of β cells. Ceramides, ROS, inflammation, and ER stress signaling are intracellular mediators of β cell failure in this context. Moreover, lipotoxicity may also impair the very limited proliferation and regeneration capacity of β cells [45], leading to an insulinopenic state.

2. Adaptive Signaling Pathways in β Cells Responding to Metabolic Distresses

In response to lipotoxicity and other metabolic challenges during obesity and diabetes, multiple molecular signaling pathways are modulated in β cells to support their function, survival, and growth. In this section, we discuss the signaling cascades mediated by insulin, mammalian target of rapamycin complex (mTORC) 1, protein kinase C (PKC) ζ , autophagy, glucagon-like peptide-1 receptor (GLP1R), peroxisome proliferator-activated receptors (PPARs), and G-protein-coupled receptor (GPR) 40, their crosstalk, and their effects on β cells.

Insulin signaling is intensively studied in β cells, especially for its prominent roles in promoting compensatory growth and functional enhancement for obesity and systemic insulin resistance [46]. The autocrine and paracrine effects of insulin on its own producing cell are interesting in light of its extremely high local concentration in islets that leaves limited room for modulation of signal intensity [47]. Loss of insulin receptor (IR) in β cells triggers diminished insulin secretion and causes type 2 diabetes [48]. It also abolishes the compensatory hyperplasia of β cells when insulin resistance is present [49]. Double knockouts of both the IR and the insulin-like growth factor 1 receptor ablate postnatal β cell mass by suppressing Akt phosphorylation and MafA expression and induction of apoptosis [50]. Immediately downstream of IR, insulin receptor substrate (IRS) 1 and IRS-2 play different roles in β cell function and survival. IRS-1 supports the transcription of insulin genes [51]. However, ablation of IRS-1 reduces the apoptosis of β cells by compensatory upregulation of IRS-2 [52], underscoring the prosurvival role of the latter. In fact, IRS-2 has been intensively studied and established as a pivotal player for β cell compensation in response to insulin resistance [53–58]. As a major downstream kinase effector of insulin signaling, Akt/protein kinase B induces key transcription factors that drive the core β cell transcriptional profile, such as Pdx-1, and promotes β cell viability [59–61]. Between the two isoforms, Akt2 is more critical for β cell survival than Akt1 [62, 63]. On the other hand, overexpression of Akt1

results in β cell hypertrophy and hyperplasia, improved glucose tolerance, and resistance to diabetes [64, 65]. Akt1 activates the cyclin-dependent kinase 4 and the promotive cyclins D1 and D2 to reignite β cell proliferation in adulthood. Cyclin D2 is critical for maintenance of adult β cell mass by marginal proliferation, and cyclin D1 supports the postnatal rapid growth of β cells together with cyclin D2 [66].

Cyclin induction by Akt is mediated through inhibition of tuberous sclerosis complex 2 and subsequent activation of the mTORC1 signaling pathway [67, 68]. Recent reports have advanced our understandings of the downstream effectors of mTORC1. S6 kinase 1, an immediate target of mTORC1, is necessary for fetal β cell growth [69]. A β cell-specific knockout of mTOR, one of the three proteins that make up mTORC1, impairs GSIS and survival of β cells, which also involves the induction of carbohydrate-responsive element-binding protein, thioredoxin-interacting protein, and oxidative stress [41]. Conditional knockout of raptor, another mTORC1 protein, also damages β cell function and viability [70]. Here, the prosurvival effects of S6 kinase 1 associate with inhibition of autophagosome formation. Eukaryotic translation initiation factor 4E (eIF4E) binding protein 2 is identified as another effector of mTORC1. Inactivation of eIF4E binding protein 2 removes the inhibition of eIF4E and supports β cell proliferation. eIF4E also increases the cap-dependent translation of carboxypeptidase E, the key enzyme for insulin processing.

PKC ζ is another inducer of mTORC1 signaling in the presence of insulin resistance. Activated by extracellular glucose and insulin, PKC ζ is necessary for the adaptive β cell proliferation mediated by mTOR and cyclin D2 but not Akt, as revealed by overexpression of a kinase dead mutant [71]. Consistent with these observations, overexpression of functional PKC ζ does not change Akt phosphorylation but upregulates mTOR phosphorylation and cyclins A, D1, D2, and D3 [72].

Autophagy is a widespread cellular process adapting to nutrient starvation or other stresses by self-degradation [73]. Similar to the UPR, the prosurvival and proapoptotic roles of autophagy can depend on the stress level and the adaptive capacity of the cell, and both prevent further tissue damage [74]. Autophagy is initiated in rodent and human islets by FFA exposure [75] and protects against death [76–78]. However, FFAs also enforce cell apoptosis by blocking the autolysosome formation step of autophagy [79, 80]. Proinflammatory cytokines, such as IL-1 β and IFN- γ , induce lysosomal dysfunction and prevent the fusion of lysosomes and autophagosomes in β cells [81], whereas IL-6 [82] and IL-22 [83] augment autophagy.

Restoration of lysosomal function and increases in autophagic flux are part of the GLP1R signaling leading to β cell survival [84]. The other prosurvival mechanisms initiated by GLP1R include crosstalk with insulin signaling via cAMP response element binding protein-induced IRS-2 upregulation [85], reversal of ER stress-induced translational attenuation [86], and nuclear translocation of PKC ζ [87]. Liraglutide, a US Food and Drug Administration-approved GLP1R agonist, has *in vitro* protective effects on β cells against FFAs or cytokine-induced apoptosis [88]. Randomized clinical trials were carried out and established the GLP1R axis as an important approach to diabetes management [89–91].

PPARs are transcriptional activators of many lipid metabolism genes [92]. PPAR γ is induced in various tissues by obesity and insulin [93] and is meant to overcome lipotoxicity [94]. Mouse β cell hyperplasia is stimulated by a conditional knockout of PPAR γ in β cells on a regular diet, but hyperplasia is suppressed on a high-fat diet [95]. The positive effects of PPAR γ on β cell function and survival are supported by many studies [96]. However, recent reports have provided *in vivo* evidence that local overexpression of PPAR γ isoforms can impair β cell mass and function in diet-induced obese (DIO) mice [97, 98], suggesting a dose-dependent effect of PPAR γ action. On the other hand, PPAR α expression in β cells is induced by fasting, leading to increased β -oxidation of FFAs and decreased insulin production [99]. Conversely, high glucose reduces PPAR α transcription and the associated PPAR α lipid metabolism [100]. In mouse β cells and human islets subjected to long-term FFA-induced lipotoxicity, overexpression of PPAR α promotes β -oxidation and esterification of FFA, as well as GSIS [101]. The *in vivo* roles of PPAR α in β cells under physiological and pathological conditions remain unclear and await further investigation.

Last but not least, short-term (minutes to hours) exposure to FFAs can paradoxically stimulate insulin secretion, which is mediated by GPR40 and intracellular Ca^{2+} signaling [102]. In the 1960s, a rapid increase in dog plasma insulin was observed after direct infusion of FFA but not triglycerides [103]. In 2003, GPR40 was first identified as a transmembrane receptor for FFAs. It potentiates β cell GSIS by facilitating the influx of extracellular Ca^{2+} [104]. *In vitro* experiments with RNA interference identified G_{α_q} , phospholipase C, sarcoplasmic reticulum calcium transport ATPase, L-type calcium channels, and the K_{ATP} channel as targets, linking GPR40 to intracellular Ca^{2+} increase [105]. GPR40 is not necessary for systemic glucose tolerance under physiological conditions and not involved in long-term FFA-impaired insulin secretion [106]. GPR40 can promote the second phase of GSIS via protein kinase D1 and remodeling of F-actin [107]. These findings support GPR40 as a promising target for diabetes drugs.

In summary, β cells use a variety of signaling pathways to handle the metabolic stresses imposed by obesity and diabetes. These short-term adaptive responses may eventually lead to favorable or unfavorable outcomes regarding β cell function and viability over the long term.

3. β Cell Adaptive Signaling Pathways in Obesity and Diabetes Interfere With Each Other

Although the adaptive signaling pathways are meant to neutralize specific detrimental effectors derived from lipotoxicity, they do not always act additively or synergistically on β cells, unfortunately. The antagonism between adaptive signaling pathways is a universal phenomenon, underlying unfavorable drug-drug interactions in many clinical therapies. Although insulin signaling in β cells is one of the most important pathways adapting cells to the increased metabolic demand in obesity and diabetes, insulin signal transduction is vulnerable to the inhibitory effects of many other signaling pathways.

The UPR is meant to alleviate ER stress, but it also impairs insulin signaling and causes insulin resistance in peripheral tissues [108, 109]. Subsequent studies have provided evidence that this also happens in β cells. Cultured β cells treated with palmitate show a concomitant increase in active c-Jun N-terminal kinase, a downstream effector of the UPR, but also a decrease in phosphorylated Akt [110]. This also happens in the β cells of diabetic *db/db* mice [111]. Pharmacological induction of ER stress and the UPR in β cells suppresses insulin signaling [111]. Interestingly, insulin signaling exerts dual effects on ER stress in β cells. Inhibition of upstream insulin signaling molecules (*e.g.*, IR and phosphoinositide 3-kinase) diminishes the sequential phosphorylation of Akt and GSK-3 β and exacerbates ER stress in tissue culture [109, 111]. In contrast, *in vivo* ablation of the phosphoinositide 3-kinase regulatory subunit p85 α in β cells reduces the nuclear translocation of XBP-1 and ameliorates ER stress in the Akita mouse model [112]. The different roles of IRS-1 and IRS-2 in β cell function and survival may be mediated by their differential actions on UPR signaling. A β cell-specific knockout of IRS-1 increases the proteasomal degradation of XBP-1 and protects against ER stress-induced apoptosis. It also facilitates the prosurvival role of the UPR by strengthening phosphorylated eIF-2 α -directed global translational attenuation. In contrast, an IRS-2 knockout in β cells increases nuclear XBP-1 and also ER stress-induced apoptosis [113]. The apparently contradictory interactions between ER stress and insulin signaling may reflect the double-edged nature of the UPR, with early prosurvival and late proapoptotic roles.

PPAR γ , the master regulator of lipogenesis, improves insulin signaling in peripheral tissues [114]. However, the crosstalk between PPAR γ and insulin signaling in β cells remains unclear. The upregulation of β cell PPAR γ by obesity and diabetes is also under control of the low-density lipoprotein receptor-related protein 1 (LRP1) [98], a transmembrane receptor and integration hub of multiple signaling pathways [115, 116]. The lack of LRP1 prompts excessive PPAR γ levels that mitigate not only lipotoxic conditions but also insulin signaling components in β cells, which eventually leads to a reduction in GSIS. Transgenic overexpression of PPAR γ in β cells on top of DIO recapitulates the unopposed PPAR γ levels

and shows impaired insulin signaling, decreased GSIS, and systemic glucose intolerance in mice with β cell specific LRP1 knockout [98]. Therefore, insulin signaling mediates the dose-dependent effect of PPAR γ on β cell function.

Collectively, the antagonistic interactions between insulin signaling and other adaptive pathways disrupt a “unified” front against lipotoxicity and other associated metabolic stresses and contribute to the eventual failure of β cells at later stages of diabetes.

4. The Potential Insulin-Sparing Effects of Diabetes Therapies

“Insulin-sparing” refers to the reduction in insulin production by antidiabetic treatment regimens. This reduction can reflect a direct action on β cell function or a secondary response to improved systemic insulin sensitivity and hence a decreased demand for insulin. Here, we focus on mechanisms supporting direct action on the β cell.

Metformin is a well-established first-line drug for management of insulin resistance and type 2 diabetes, and its insulin-sparing effect has raised concerns since the 1990s [117, 118]. As an inhibitor of the mitochondrial enzyme glycerol-3-phosphate dehydrogenase, metformin blocks gluconeogenesis from liver [119] and kidney [120]. Through ATP depletion, metformin also activates AMP-activated protein kinase (AMPK), a key homeostat of intracellular energy, in multiple tissues [121, 122]. AMPK promotes β -oxidation of FFAs by facilitating their translocation from cytosol into mitochondria [123]. However, the AMPK solution to lipotoxicity is at the price of β cell dysfunction. Adenoviral overexpression of active AMPK in rodent islets results in decreased GSIS and increased apoptosis, which can be reversed by overexpression of a dominant negative mutant of AMPK [124]. AMPK inhibition by elimination of its activating kinase liver kinase B1, on the other hand, supports β cell growth and insulin secretion [125]. Overexpression of an active liver isoform of carnitine palmitoyl-transferase I, the downstream effector of AMPK, increases β -oxidation of FFAs but impairs GSIS in β cells [126]. It is possible that the insulin-sparing effects of metformin are masked by the improved systemic insulin sensitivity and reduced demand on insulin production. But this does not preclude the combination of insulin and metformin in treating diabetes [127–129].

Insulin-sparing effects were also observed with thiazolidinediones, a class of PPAR γ agonists decreasing insulin transcription and secretion in rat islets [130]. Although clinical trials showed PPAR γ agonists can increase β cell function in patients with type 2 diabetes [131, 132], such an increase cannot be pinpointed as a primary effect on β cells, because it could be secondary to the improved systemic lipid metabolism. In the setting of diabetes, thiazolidinediones may induce PPAR γ activity to a supraphysiological level in β cells, which in turn may diminish insulin signaling and GSIS [97, 98]. Although the physiological roles of PPAR α in β cells are largely unknown, fenofibrate, a PPAR α agonist, protects β cells from lipotoxicity in obese rats [133] but reduces basal and stimulated insulin secretion in primary human islets [134]. This again reflects the dichotomous results of PPAR α action, similar to what is seen for PPAR γ .

Agonists for adiponectin receptors are a class of promising drugs for diabetes and the metabolic syndrome [135]. As a well-known metabolically beneficial adipokine, adiponectin exerts pleiotropic actions via the widely expressed adiponectin receptor 1 (AdipoR1) and AdipoR 2 [136, 137]. AdipoR1 and AdipoR2 activate AMPK and PPAR α signaling, respectively, in peripheral tissues [138]. Meanwhile, they both degrade intracellular lipotoxic sphingolipids by their intrinsic ceramidase activity [20], which is supported by their crystal structures [139]. AdipoR1 and AdipoR2 are expressed in β cells of human and rodents [140], and the antilipotoxic effects of adiponectin preserve the β cell mass in insulinopenic diabetes [8, 141]. However, during the progression of insulin resistance and type 2 diabetes, downstream AMPK and PPAR α activation may raise concerns about the potential insulin-sparing effects of AdipoR agonists. AdipoRon, a recently discovered small molecule, activates AdipoRs and improves insulin sensitivity of muscle and liver in DIO mice, mimicking the function of adiponectin [142]. It stimulates AMPK activity in cardiomyocytes [143] and protects liver,

adipose, and kidney via the ceramidase activity of AdipoRs [144, 145]. As for β cells in obesity and diabetes, the functions of AdipoR signaling need a delicate assessment. A selective agonist to specifically increase the ceramidase activity of AdipoRs may circumvent the potential insulin-sparing effects of AMPK and PPAR α signaling, but it is not clear whether such a selective activity with regard to the downstream activation of signaling components can be achieved.

5. Conclusions

Lipotoxicity associated with obesity and type 2 diabetes provides insults to β cells via multiple causative agents, including ceramides, ROS, inflammation, and ER stress. β cells are able to use multiple adaptive pathways to protect against lipotoxicity and other metabolic stresses (Fig. 1). However, some of these pathways are not always synergistic and can eventually lead to the demise of the function and viability of β cells. An analogy could be drawn to a scenario in which a fire is extinguished and the collateral damage is the flooding of the premises caused by excessive water use. We could therefore refer to the phenomenon as the “lipo-fighter’s dilemma.” As a concept, it can explain the insulin-sparing effects of some diabetic drugs, but it may also be generalized to many other adaptive processes in the body.

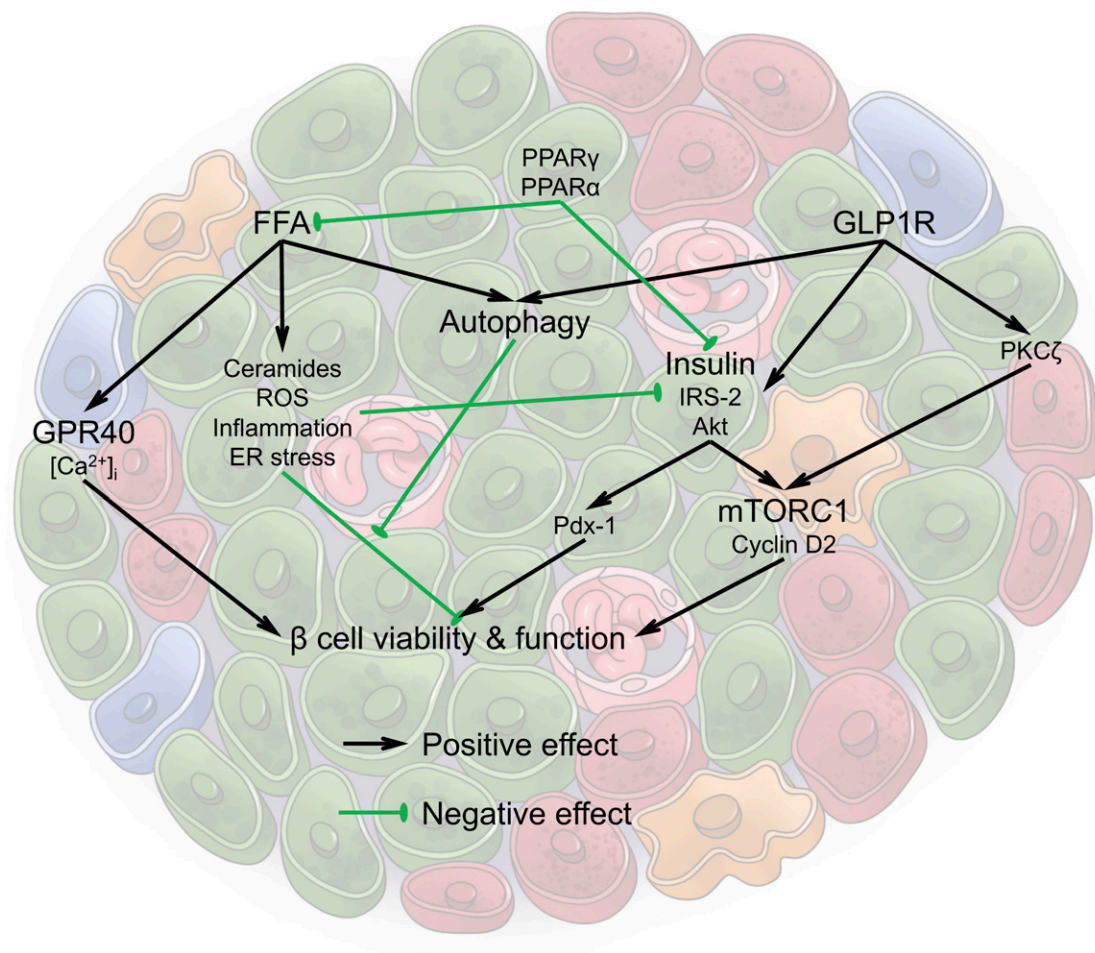


Figure 1. Multiple pathways interact as part of an antilipotoxic response, with some pathways exerting a positive effect (in black) and other pathways leading to a repressive effect (indicated in green) in the β cells in the islet. See text for details on the individual pathways mentioned and how they interact.

6. Search Strategies

Combinations of the following terms were searched on PubMed and Google: lipotoxicity, lipid metabolism, obesity, diabetes, metabolic syndromes, muscle, heart, liver, kidney, beta cells, islets, insulin secretion, insulin expression, proliferation, hyperplasia, growth, hypertrophy, dysfunction, apoptosis, death, human, mouse, nutrient, lipid, glucose, fatty acids, beta oxidation, lipogenesis, glucolipotoxicity, hyperlipidemia, ceramides, lipotoxic sphingolipids, oxidative stress, ROS, inflammation, NF κ B, ER stress, UPR, pro-survival, pro-apoptotic, insulin signaling, knockout, overexpression, insulin receptor, IRS, Akt, mTOR, mTORC1, S6K, cyclin, PKC zeta, autophagy, lysosome, GLP-1, extendin, CREB, Pdx-1, MAPK, Erk, liraglutide, clinical trial, PPAR gamma, TZD, PPAR alpha, fibrate, GPR40, Ca²⁺, calcium, JNK, PI3K, insulin sparing effect, metformin, AMPK, CPT, ACC, malonyl-CoA, acetyl-CoA, mitochondria, Lkb, adiponectin, adiponectin receptor, AdipoRon, ceramidase.

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