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Mini review

Islet β-cell failure in type 2 diabetes – Within the network of toxic lipids

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ABSTRACT

Obesity-related type 2 diabetes develops in individuals with the onset of β-cell dysfunction. Pancreatic islet lipotoxicity is now recognized as a primary reason for the onset and progression of the disease. Such dysfunction is reflected by the aberrant secretory capacity and detrimental loss of β-cell mass and survival. Elevated circulating serum fatty acid levels and disordered lipid metabolism management are particularly interesting in the search for biologically relevant triggers of β-cell demise. Herein, we review various types of toxic lipid metabolites that may play a significant role in pancreatic islet failure. The lipotoxic effect on β-cells depends on the type of lipid mediator (e.g., long-chain fatty acids, diacylglycerols, ceramides, phospholipids), cellular location of its action (e.g., endoplasmic reticulum, mitochondria), and associated-organelle conditions (e.g., membranes, vesicles). We also discuss various aspects of lipid action in β-cells, including effects on metabolic pathways, stress responses (e.g., oxidative stress, endoplasmic reticulum stress, and autophagy), and gene expression.

1. Introduction

Increases in the circulating levels of plasma fatty acids (FAs) and disturbances in lipid metabolism regulation are commonly associated with obesity and serve as the most plausible factors that contribute to progressive β-cell dysfunction and loss in type 2 diabetes (T2D) [1]. Fatty acids induce a pleiotropic effect on β-cell function, including changes in cell signaling, insulin secretion, mitochondria metabolism, and membrane composition. The acute accumulation of FAs enhances insulin release. The long-term exposure of islets to FAs severely impairs glucose-stimulated insulin secretion (GSIS), drives the suppression of proinsulin synthesis, and decreases insulin stores, leading to apoptosis [2]. The ultimate effects of specific FAs on insulin secretion and rates of β-cell death are directly related to the degree of their saturation and carbon chain length. Chronic treatment of β-cells with unsaturated FAs, such as arachidonic acid, increases GSIS and β-cell survival [3]. Endocannabinoids (arachidonate derivatives) stimulate insulin secretion in INS-1E cells through cytoskeletal reorganization [4]. However, prolonged exposure to palmitate inhibits the secretory capacity of β-cells and impairs insulin gene expression by decreasing the activity of its promoter or diminishing the binding of pancreas duodenum homeobox-1 and MafA transcription factors to the preproinsulin gene-flanking sequence [5].

A recent study showed that human pancreatic islets that were exposed to palmitate exhibited dysregulation in gene expression and DNA methylation in 141 genes that are involved in insulin signaling and 41 lipid metabolism-related genes [6]. Additionally, the inhibition of stearoyl-CoA desaturase, an important enzyme in the regulation of palmitate metabolism and insulin sensitivity [7], was shown to reduce the level of DNA methylation in 3T3-L1 cells [8]. Fatty acids might also control the activity of transcription factors by specifically binding to nuclear receptors or regulating mRNA turnover and nuclear abundance. For example, FAs are natural ligands and activators of peroxisome proliferator-activated nuclear receptors (PPARs), and PPARγ was shown to attenuate GSIS and facilitate the further harmful accumulation of neutral lipids in β-cells that were subjected to an increase in FA challenge [9]. PPARα and PPARδ were reported to preserve GSIS and stimulate FA β-oxidation in both islets and insulinoma cells [10,11]. Fatty acids also affect β-cell function via cell-surface G-protein-coupled receptors (GPCRs), such as GPR40 [12]. Fatty acids were shown to activate

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Abbreviations

AIF	apoptosis-inducing factor
ATP	adenosine triphosphate
Bak	Bcl-2 homologous antagonist killer
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
CHOP	C/EBP homologous protein
DAG	diacylglycerol
ER	endoplasmic reticulum
ETC	electron transport chain
FA	fatty acid
GPCR	G-protein-coupled receptor
GSIS	glucose-stimulated insulin secretion
iPLA$_2\beta$	Ca^{2+}-independent phospholipase A2
JNK	c-Jun NH_2-terminal kinase
LC3B II	microtubule-associated protein 1 light chain 3B II
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PPAR	peroxisomal proliferator-activated nuclear receptor
ROS	reactive oxygen species
SERCA	sarco/endoplasmic reticulum Ca^{2+}-ATPase
SMase	sphingomyelinase
T2D	type 2 diabetes
tBid	truncated BH3 interacting-domain death agonist
UCP2	uncoupling protein-2
UPR	unfolded protein response

K_{ATP}-dependent channels in β-cells, causing potassium leakage and decreasing GSIS [13]. Furthermore, prolonged treatment with FAs triggered the diffusion of Ca^{2+} channels and loss of their co-localization with secretory granules [14].

Ectopic fat spill-over subsequently enters non-oxidative pathways where more toxic and reactive FA derivatives, such as ceramides or secondary messengers (e.g., diacylglycerol [DAG]), are produced [15]. Several molecular processes clarifying the mechanism of lipotoxicity in β-cells have been suggested, including endoplasmic reticulum (ER) stress, alterations in mitochondrial function, the generation of reactive oxygen species (ROS), the synthesis of *de novo* ceramide, and insufficient autophagy (Fig. 1) [16]. We review herein the latest advances in our understanding of the role of lipids in the control of pancreatic islet metabolism and the involvement of their toxic derivatives in the pathogenesis of pancreatic β-cell dysfunction.

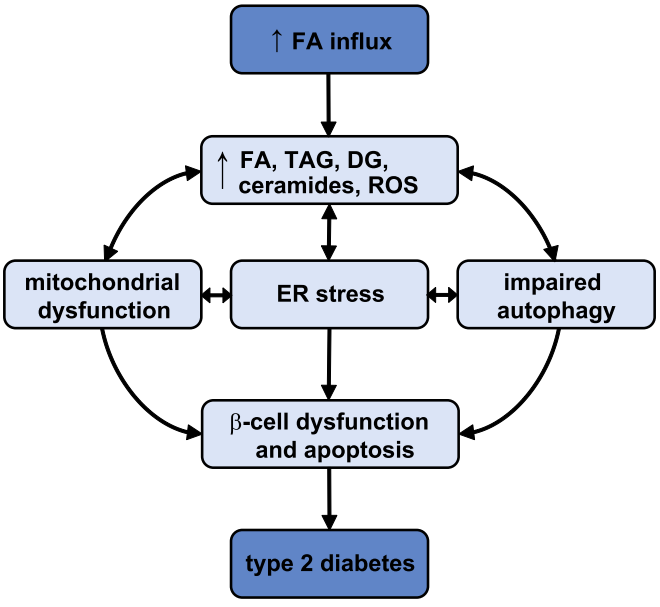

Fig. 1. Lipid-induced β-cell failure in type 2 diabetes. Chronic oversupply of fatty acids (FA) triggers the synthesis of toxic derivatives, such as diacylglycerol (DAG), triacylglycerol (TG), ceramides, and reactive oxygen species (ROS). These lipid species initiate several undesirable molecular processes in β-cells, including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and insufficient autophagy. These phenomena promote β-cell failure and initiate apoptosis, a sequence of events that leads to the development of type 2 diabetes.

2. Endoplasmic reticulum stress

Insulin that is secreted by pancreatic β-cells represents more than 50% of their total protein synthesis, and the ER accounts for half of this production [17]. The great secretory demand requires a very well-developed and highly active ER. Pancreatic β-cells are particularly sensitive to ER stress and subsequent activation of the unfolded protein response (UPR).

Endoplasmic reticulum stress markers were shown to be elevated in pancreatic islets in animal models of diabetes and in patients with T2D [18]. Lipotoxic ER stress slightly differs from the classic UPR, mainly through the independent modulation of downstream pathways and the mode of its activation. Fatty acid-induced ER stress arises particularly via the disruption of protein processing and trafficking [19] or incorrect Ca^{2+} regulation [20]. Perturbations in the ER milieu, such as alterations in Ca^{2+} compromise overall folding capacity and trigger the ER stress response. Recent studies reported that although palmitate was able to induce ER stress via ER Ca^{2+} depletion, it did not lead to protein misfolding, whereas the sarco/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase (SERCA) pump inhibitor thapsigargin caused protein misfolding (Fig. 2) [21]. Additionally, compensatory increases in proinsulin biosynthesis in an attempt to overcome insulin resistance, triggered by saturated FAs, are unable to evoke terminal ER stress. A moderate ER stress response that is induced by proinsulin overexpression is consistent with this adaptive response [22]. Protein overload, however, might also result from the impaired exiting of protein from the ER, in opposition to augmented biosynthesis. Indeed, the use of temperature-sensitive reporter constructs enabled several groups to convincingly demonstrate the disruption of ER-to-Golgi trafficking that occurs as a result of lipotoxicity [23]. Independent confirmation of the theory of impaired protein trafficking came from studies, demonstrating inhibited budding of ER-derived vesicles, found in pancreatic β-cells chronically exposed to saturated FAs [24].

Several mechanisms have been proposed to underlie protein folding or trafficking that is compromised by FAs. Increases in either cholesterol or the phosphatidylcholine:phosphatidylethanolamine (PC:PE) ratio in the ER membrane were suggested to disrupt SERCA activity [25]. Additionally, a general decrease in membrane phospholipid unsaturation, particularly with regard to the ER membrane, might impair the structure of this organelle and possibly the budding of secretory vesicles [26]. Recent findings, however, have drawn attention to sphingolipid metabolism, the alterations of which are more likely involved in impaired protein trafficking, and enhanced ER stress that is linked to lipoapoptosis. Interestingly, selective and ER-localized declines in both

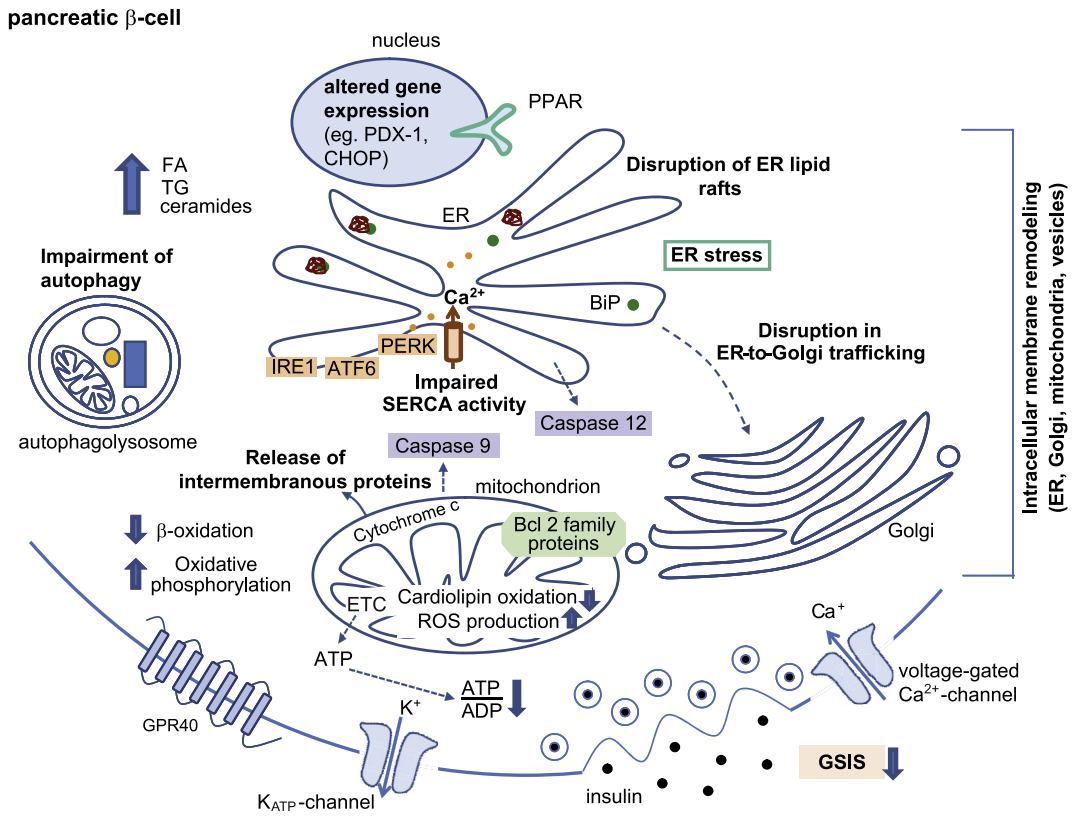

Fig. 2. Schematic overview of the major lipotoxic pathways in pancreatic β-cells. Chronic exposure to elevated levels of FAs causes β-cell dysfunction, which contributes to the development of T2D. The intracellular mechanisms that are involved in β-cell impairment include metabolic interference, membrane disruption (ER, mitochondria, vesicles), and cellular stress responses, such as mitochondrial oxidative stress, ER stress, and presumably autophagy. Moreover, long-term FA exposure leads to a decrease in ATP production, thus suppressing glucose-stimulated insulin secretion (GSIS). Abbreviations: GPR40, G-protein-coupled receptor 40; ETC, electron transport chain.

sphingomyelin and free cholesterol (which lead to the disruption of ER lipid rafts), rather than increases in ER ceramide, have emerged as a toxic mechanism [24]. Lipid rafts are involved in the loading of cargo into secretory vesicles, and lipid raft alterations that accompany chronic saturated FA exposure may provide a unique explanation for concomitant protein overload and ER stress [27].

In situations of prolonged ER stress, the UPR fails to resolve protein-folding defects and may eventually lead to apoptosis. The ER can sense and transmit apoptotic signals in β-cells in response to lipotoxicity [19,28]. There are several broad mechanisms by which lipotoxic β-cell death might be triggered downstream of ER stress, including the transcriptional induction of C/EBP homologous protein (CHOP)/GADD153, activation of c-Jun NH_2-terminal kinase (JNK), and activation of caspase-12.

3. Mitochondrial dysfunction

An impaired secretory response to glucose in pancreatic β-cells from T2D subjects was shown to be correlated with considerable modifications of mitochondrial function and morphology. Under low-glucose conditions, FA catabolism via mitochondrial β-oxidation serves as a significant source of ATP for pancreatic β-cells [29]. Several lines of evidence suggest that increases in β-oxidation and oxidative phosphorylation, associated with obesity and hyperglycemia, induce lipotoxicity by augmenting the production of ROS in mitochondria [30]. Under normal physiological conditions, only 0.1% of total oxygen consumption leads to ROS generation, which results from imperfect electron transport [31]. However, the magnitude of this leakage increases under various pathological conditions, including diabetes [32]. Mitochondria are the main source of ROS and also the primary target of their action. The main submitochondrial localization of ROS formation is the inner mitochondrial membrane. Therefore, its components are at high risk of oxidative injury. Insulin-producing cells are known for their limited antioxidant capacity. Thus, a persistent imbalance between excessive ROS formation and restricted antioxidant defenses leads to oxidative stress, which can eventually damage mitochondria and cause β-cell death [33]. The chronic exposure of rat pancreatic islets to oleate and palmitate was reported to induce apoptosis. This effect was prevented by nicotinamide, indicating that the cytotoxic effects of elevated FAs can be mediated by oxidative stress [16].

Nevertheless, little is known about the mechanisms that trigger mitochondria-dependent apoptosis in β-cells. Proapoptotic stimuli promote the release of intermembranous proteins, including cytochrome c and apoptosis-inducing factor (AIF) into the cytoplasm, and consequently the formation of so-called apoptosomes. The initiator caspase-9 becomes activated, which in turn activates executioner caspases-3, -6, and -7. Cytochrome c release is thought to be the key step in the initiation of apoptosis, and appears to result from a direct action of ROS on the inner mitochondrial membrane phospholipid cardiolipin [34]. During the early phase of apoptosis, ROS production is stimulated and cardiolipin is oxidized, thus weakening the interaction with cytochrome c and its subsequent release into the cytoplasm (Fig. 2). The particular susceptibility of cardiolipin to oxidation results from its enrichment with polyunsaturated FA residues, notably linoleate and arachidonic acid [35]. Moreover, mitochondrial cardiolipin is also a target of the proapoptotic B-cell lymphoma 2 (Bcl-2) family protein member truncated BH3 interacting-domain death agonist (tBid), which facilitates pore formation in the outer mitochondrial membrane by

two other proapoptotic members, Bcl-2-associated X protein (Bax) and Bcl-2 homologous antagonist killer (Bak) [36].

4. Ceramides: at the crossroads between the endoplasmic reticulum and mitochondria

Obesity-associated increases in FAs with simultaneous restraint of their β-oxidation drives the accumulation of FA-CoA, which in turn can be esterified into complex lipids, such as ceramides and DAG, and directly contribute to pancreatic islet dysfunction and lipotoxicity [1]. In pancreatic β-cells, ceramides are one of the most important mediators of FA-derived β-cell failure and apoptosis, but the precise mechanism of action remains far from clear [27]. The toxic effect of ceramides on β-cells was reported to occur mainly through the promotion of their *de novo* synthesis [37]. Inhibitors of ceramide synthesis act at the level of either serine palmitoyltransferase (L-cycloserine) or ceramide synthase (fumionisin B1) and block the deleterious effects of palmitic acid on β-cell viability [23]. Additionally, ceramide accumulation diminishes proinsulin mRNA levels in isolated islets. Through oxidative stress- and c-jun-dependent pathways, JNK mitigates *Ins* gene transcription [38]. Another possibility is that ceramide directly activates protein kinase C ζ, thus inhibiting the transcriptional activity of PDX-1 [39].

Although the effect of *de novo*-synthesized ceramides on FA-induced β-cell dysfunction is well documented [37], the involvement of the sphingomyelin signaling pathway cannot be excluded. Ca^{2+}-independent phospholipase A2 ($iPLA_2\beta$), an inducer of β-cell apoptosis in response to acute ER stress, was shown to promote the generation of ceramides via the hydrolysis of sphingomyelin in an INS-1 cell line, whereas the administration of a neutral sphingomyelinase (SMase) inhibitor reversed the aforementioned effect. Furthermore, $iPLA_2\beta$-derived ceramide generation in β-cells was linked to ER stress-associated mitochondrial dysfunction and activation of the intrinsic apoptotic pathway [40].

Alterations in mitochondrial membrane integrity by ceramide were also proposed to induce apoptosis in β-cells [23]. The activation of SMase led to the induction and translocation of the pro-apoptotic protein Bax to mitochondria, with simultaneous cytochrome c leakage into the cytosol [41]. Additionally, ceramide decreased the mRNA expression of the antiapoptotic molecule Bcl-2 [39], and caspases 3/7 were activated in rodent insulinoma β-cells during sphingolipid-mediated cell death [37]. Furthermore, the overexpression of ceramide synthase 4 in INS-1E cells potentiated the palmitate- and stearate-induced accumulation of ceramides and enhanced apoptosis through the production of specific ceramide species with such residues as C18:0, C22:0, and C24:1 [37]. Therefore, one postulation may be that ceramide is a lipid second messenger that is involved in the cross-talk between the ER and mitochondria.

5. Defective autophagy

Macroautophagy (henceforth referred to as autophagy) is a strongly dynamic process that plays a major role in the elimination of pathogens, dysfunctional organelles, and protein aggregates through lysosomal machinery because they are deleterious or because of nutrient deficiency. Under normal growth conditions, a low level of constitutive autophagy is usually sustained for cellular quality control purposes; when stress stimuli occur, autophagy is believed to serve as a survival mechanism [42].

A fairly new research direction has demonstrated reciprocal communication between the autophagic pathway and intracellular lipids in pancreatic islets. Insulin is a well-known hormonal suppressor of autophagy. Type 2 diabetes particularly depends on the metabolism of nutrients, and the action of insulin and impairment of autophagy may play roles in the pathogenesis of T2D. Basal autophagy appears to be indispensable for the architecture, viability, and proper physiology of pancreatic β-cells [43]. Mice with selective deficiency in autophagy (i.e., mice with β-cell-specific knockout of *Atg7*) displayed impaired glucose tolerance. Furthermore, increased apoptosis, decreased proliferation, impaired insulin secretion, the accumulation of protein aggregates, and damaged organelles were confirmed in β-cells in the absence of autophagy [44]. Interestingly, a substantial number of autophagosomes was reported in ZDF rats [45], *db/db* mice, and C57BL/6 mice that were challenged with a high-fat diet [44].

Additional supporting evidence has been provided by *in vitro* studies. INS-1E cells that were exposed to oleate or palmitate at different time points exhibited the induction of autophagosomes, confirmed by increases in microtubule-associated protein 1 light chain 3B II (LC3B-II) levels [46] The induction of autophagosomes was accompanied by the inhibition of autophagic turnover and impairment in lysosomal acidification when INS-1E cells were subjected to long-term palmitate exposure [47]. Furthermore, the activation of autophagy was shown to play a protective role in the palmitate-induced death of INS-1E cells [48]. The *ex vivo* exposure of pancreatic islets from non-diabetic individuals to a combination of palmitate and oleate resulted in autophagic vacuole accumulation and an increase in apoptosis [49].

When *Atg7*-deficient animals were fed a high-fat diet, they suffered severe glucose intolerance, together with a pronounced failure in the compensatory increase in β-cell mass and an increase in the accumulation of caspase-3-positive apoptotic cells [44]. Furthermore, electron microscopic analysis of pancreatic islets from T2D cadavers confirmed the presence of abnormally overloaded autophagosomes that was likely attributable to impaired lysosome formation [49]. These observations support the hypothesis that compromised autophagic activity renders β-cells more susceptible to lipotoxicity and can predispose individuals to T2D. Further corroborating this possibility, the presence of functionally defective, malformed mitochondria and cisternal distension of the ER appeared to contribute to the reduction of the insulin secretory capacity of autophagy-deficient β-cells [44]. Palmitate and oleate treatment-induced increases in UPR gene expression in control islets were compromised when autophagy-deficient β-cells were employed instead [50]. Therefore, under states of insulin resistance and at high serum FA concentrations, the bulk of harmful protein aggregates and organelles in β-cells needs to be eliminated through effective autophagic machinery [43]. Maintenance of the quality of the ER and mitochondria in insulin-secreting β-cells is critical for their survival and a selective target of organelle-specific macroautophagy, referred to as reticulophagy and mitophagy, respectively [50,51].

6. Concluding remarks

Concern about the pandemic incidence of diabetes is increasing because of the high prevalence of individuals who are overweight or obese, which has a negative impact on quality of life and healthcare. Type 2 diabetes is recognized as a progressive multisystemic disorder that considerably affects the function of the liver, heart, and kidneys. Evidence indicates that β-cell failure is a central contributor to the onset and progression of the disease. The mechanisms that underlie pancreatic β-cell lipotoxicity and dysfunction are coupled with a wide range of changes at the level of genes and proteins. However, these general findings merely reveal an entire network of biochemical pathways and molecular mechanisms that underlie the lipid-derived physiology of islet adaptive transitions (Fig. 2). The final effect on β-cell mass, function, and survival depends on the specific lipid species, its cellular site of

action, and condition of organelles that are engaged in executing biological sequelae. The processes that are discussed in this review and the lipids that participate in the dysfunction of insulin-secreting cells are not mutually exclusive. They are highly interconnected, and the activation of one likely triggers another, leading to a cascade of damage. Therefore, any therapeutic approach that is based on inhibiting or perturbing specific pathways that are affected by lipotoxicity to prevent and treat β-cell collapse in T2D should be carefully considered within the framework of investigating and developing new therapies and for the sake of patients' clinical expectations.

Conflict of interest

The authors declare that they have no conflicts of interest.

Statement of human and animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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