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Review

Beta-cell mitochondrial carriers and the diabetogenic stress response☆

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ABSTRACT

Mitochondria play a central role in pancreatic beta-cells by coupling metabolism of the secretagogue glucose to distal events of regulated insulin exocytosis. This process requires transports of both metabolites and nucleotides in and out of the mitochondria. The molecular identification of mitochondrial carriers and their respective contribution to beta-cell function have been uncovered only recently. In type 2 diabetes, mitochondrial dysfunction is an early event and may precipitate beta-cell loss. Under diabetogenic conditions, characterized by glucotoxicity and lipotoxicity, the expression profile of mitochondrial carriers is selectively modified. This review describes the role of mitochondrial carriers in beta-cells and the selective changes in response to glucolipotoxicity. In particular, we discuss the importance of the transfer of metabolites (pyruvate, citrate, malate, and glutamate) and nucleotides (ATP, NADH, NADPH) for beta-cell function and dysfunction.
This article is part of a Special Issue entitled: Mitochondrial Channels edited by Pierre Sonveaux, Pierre Maechler and Jean-Claude Martinou.

1. Introduction

1.1. Insulin secretion from the β-cell

Glucose homeostasis relies on the functioning of pancreatic β-cells that compose only 0.01% of our body. These essential insulin-secreting cells are located within the islets of Langerhans, which represent the endocrine fraction of the pancreas [1]. Pancreatic β-cells exhibit neuroendocrine characteristics with the unique feature of responding to glucose, the most common nutrient, as the main stimulus for regulated exocytosis of the hormone insulin. This requires tight coupling between products of glucose metabolism and action on cell membrane channels triggering insulin release. Connection between these proximal glycolytic and distal exocytotic events is ensured by the mitochondria. Such pivotal role involves carriers mediating specific transports in and out of the mitochondria. The mitochondrial transporter family has been scrutinized quite intensively over the last years, defining new properties and links with diseases [2,3].

Glucose metabolism generates pyruvate, in turn activating mitochondria and promoting ATP formation. Export of ATP from the mitochondria to the cytosolic compartment induces the closure of ATP-sensitive K^+-channels (K_{ATP}-channel) on the plasma membrane and, as a consequence, depolarization of the cell [4]. This leads to Ca^{2+} influx through voltage-gated Ca^{2+} channels and a rise in cytosolic Ca^{2+} concentrations (Fig. 1), which is the main and necessary signal for exocytosis of insulin [5]. Additional signals are required to sustain the secretion elicited by glucose-induced Ca^{2+} rise. They participate in the amplifying pathway, also referred to as the K_{ATP}-channel independent stimulation of insulin secretion [6], which requires integration and generation of metabolic signals by the mitochondria [7]. This role is additive to the generation of ATP necessary for the elevation of cytosolic [Ca^{2+}]. The most studied additive factors proposed to amplify the Ca^{2+} signals are cAMP, glutamate, NADPH, long chain acyl-CoA derivatives, and superoxides.

The present review describes advances that have been made in the recent years related to β-cell mitochondrial carriers, both in healthy situation and in the context of type 2 diabetes.

1.2. Insulin secretion and the diabetic β-cell

Among the patients suffering from diabetes mellitus, the large majority is classified as type 2 diabetes, or non-insulin-dependent diabetes. The patients display dysregulation of insulin secretion, often combined with resistance of target tissues to insulin signalling. The aetiology of type 2 diabetes is still poorly understood; in particular when the disease is associated with obesity, although it became clear over the last years that β-cell impairment is a triggering event on a background of insulin resistance [8,9]. In some type 2 subtypes, diabetes is primarily induced by β-cell dysfunction, i.e. maturity onset diabetes of the young (MODY) and mitochondrial diabetes, both linked to specific gene mutations [10–13]. The impact of such mutations on the β-cell highlights the importance of the mitochondria in the control of insulin secretion. In the case of obesity-associated diabetes, several cellular factors have been proposed, also pointing to mitochondrial dysfunction of the β-cell [14].

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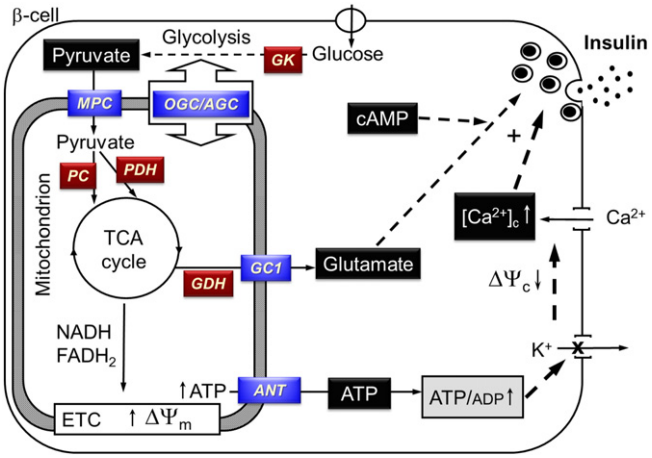

Fig. 1. Model for coupling of glucose metabolism to insulin secretion in the β-cell. Glucose equilibrates across the plasma membrane and is phosphorylated by glucokinase (*GK*). Further, glycolysis produces pyruvate, which preferentially enters into mitochondria through MPC and fuels the TCA cycle by the action of both pyruvate dehydrogenase (PDH) and pyruvate carboxylase (PC). The malate/aspartate shuttle (OGC/AGC) transfers cytosolic NADH-derived reducing equivalents into the mitochondria. The TCA cycle generates reducing equivalents transferred by NADH and $FADH_2$ to the electron transport chain (ETC), leading to hyperpolarization of the mitochondrial membrane ($\Delta\Psi_m$) and generation of ATP. Then, ANT transfers ATP to the cytosol, raising the ATP/ADP ratio. Subsequently, closure of K_{ATP}-channels depolarizes the cell membrane ($\Delta\Psi_c$). This opens voltage-dependent Ca^{2+} channels, increasing cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$), which triggers insulin exocytosis. The amplifying pathway of metabolism-secretion coupling is contributed by additive coupling factors, e.g. glutamate produced by glutamate dehydrogenase (GDH) and transported by GC1.

2. Metabolism–secretion coupling in β-cells

2.1. From glucose entry to mitochondria

In β-cells, metabolism–secretion coupling refers to both the consensus model and the contribution of additional coupling factors, i.e. the trigger and amplifying pathways of glucose-stimulated insulin secretion (Fig. 1). This process is initiated by gradient-driven entry of glucose within the β-cell across the plasma membrane through GLUT2 and its subsequent phosphorylation by glucokinase, thereby fuelling glycolysis [15]. In the cytosolic compartment, glycolysis extracts reducing equivalents transmitted to NADH. Maintenance of the glycolytic flux requires reoxidation of NADH to NAD^+ to avoid arrest of glycolysis.

In most tissues, cytosolic conversion of pyruvate to lactate by the lactate dehydrogenase ensures NADH re-oxidation to NAD^+, while in β-cells this task is devoted mainly to mitochondrial NADH shuttles, transferring glycolysis-derived electrons to mitochondria.

2.2. The mitochondrial NADH shuttle system

The mitochondrial NADH shuttle system is composed of the glycerophosphate and the malate/aspartate shuttles. A key component of the former is the mitochondrial enzyme glycerol phosphate dehydrogenase (mGPDH). Mice lacking mGPDH exhibit a normal phenotype and their islets respond normally to glucose stimulation regarding metabolic parameters and insulin secretion [16]. Additional abrogation of the malate/aspartate shuttle by the transaminase inhibitor aminooxy acetate (AOA) in these mGPDH-null islets strongly impairs the secretory response to glucose [16]. This indicates that the main role is played by the malate/aspartate shuttle (Fig. 1), as suggested earlier by the first studies making use of AOA in pancreatic islets [17,18]. Of note, effects of AOA are much stronger in rat [17,18] compared to mouse [16,19] islets. Besides cytosolic and mitochondrial transaminases, the malate/aspartate shuttle requires two mitochondrial metabolite carriers, namely the aspartate–glutamate carrier (AGC) and 2-oxoglutarate carrier (OGC) (see Table 1).

Suppression of the α-ketoglutarate–malate exchanger OGC in pancreatic β-cells decreases glucose-stimulated insulin secretion [20,21]. In insulinoma INS-1 832/13 cells, a marked reduction of the secretory response is achieved by both knockdown of OGC [20] and its inhibition by phenyl succinate [21]. However, in primary cells insulin release is marginally affected by OGC knockdown in rat islets [20] and no effects at all are observed in mouse islets treated with phenyl succinate [21].

The other member of the malate/aspartate shuttle is the Ca^{2+}-sensitive aspartate–glutamate exchanger AGC1, also named Aralar1 [22]. Its general abrogation results in severe growth retardation, attributed to the observed impaired central nervous system function [23]. In pancreatic β-cells, overexpression of AGC1 increases glucose-induced mitochondrial activation and secretory response [24]. This is accompanied by enhanced glucose oxidation and reduced lactate production. In insulinoma INS-1E cells, the mirror experiment consisting of silencing AGC1 reduces glucose oxidation and the secretory response, although primary rat β-cells are not sensitive to such a manoeuvre [25].

Therefore, the malate/aspartate system appears to set a limit for NADH shuttle function and mitochondrial metabolism, exhibiting cell type-specific dependence (Fig. 1).

2.3. The fate of pyruvate and mitochondrial activation

The importance of the NADH shuttle system illustrates the tight coupling between glycolysis and mitochondrial activation in β-cells, favouring transfer of pyruvate into mitochondria over lactate production. Accordingly, activities of both lactate dehydrogenase and monocarboxylate transporter are low in β-cells, thereby limiting lactate formation and release of glucose-derived metabolites from the cell [26]. It is therefore not surprising that the mitochondrial pyruvate

Table 1
Main metabolite carriers described to play a role in pancreatic β-cells.

Metabolite (abbreviation, number of carbons)	Symbol	Carrier	Transport type	Reference
Pyruvate (Pyr, C3)	BRP44	MPC	Exchanger (OH^-)	[28,29]
Malate (Mal, C4)	SLC25A1	CIC	Exchanger (Mal^-/Cit^-)	[125]
	SLC25A10	DIC	Exchanger (Pi)	[120]
	SLC25A11	OGC	Exchanger ($Mal^-/\alpha KG^-$)	[20]
	SLC25A8	UCP2	Exchanger (Pi)	
Oxaloacetate (OA, C4)	SLC25A8	UCP2	Exchanger (Pi)	[117]
Aspartate (Asp, C4)	SLC25A12	AGC1	Exchanger (Asp^-/Glu^-)	[24,25]
Glutamate (Glu, C5)	SLC25A22	GC1	Cotransporter (H^+),	[81]
	SLC25A12	AGC1	Exchanger (Glu^-/OH^-)	[24,25]
			Exchanger (Glu^-/Asp^-)	
α-Ketoglutarate (αKG, C5) *or 2-oxoglutarate (2OG)*	SLC25A11	OGC	Exchanger ($\alpha KG^-/Mal^-$)	[20]
Citrate (Cit, C6)/isocitrate	SLC25A1	CIC	Exchanger (Cit^-/Mal^-)	[125]

carrier (MPC), identified rather recently [27], plays a necessary role in β-cells (Table 1). MPC forms a heterodimer composed of MPC1 and MPC2 and both are expressed in pancreatic β-cells [28]. Down-regulation of either MPC1 or MPC2 inhibits glucose-stimulated insulin secretion [28]. The essential role of MPC for β-cell function is also illustrated by mice expressing an N-terminal truncated MPC2 protein [29]. These Mpc2Δ16 mice have reduced capacity for mitochondrial pyruvate oxidation and exhibit hyperglycaemia after a glucose challenge. Islets isolated from Mpc2Δ16 mice have impaired glucose-stimulated insulin secretion, although the secretory response to Ca^{2+}-raising agents is preserved [29]. These recent data demonstrate what was anticipated long ago, i.e. glucose-derived pyruvate must be transported into mitochondria in order to induce mitochondrial activation resulting in ATP generation. Although mitochondria also oxidize fatty acids and amino acids, glucose-derived metabolites are the most important fuel under physiological conditions for the β-cell.

3. Mitochondrial activation in β-cells

3.1. Activation of mitochondria by metabolites

Pyruvate entry within the mitochondria induces metabolic activation of this organelle. There, pyruvate either loses one carbon to generate acetyl-CoA or gains one carbon to form oxaloacetate; reactions catalyzed by pyruvate dehydrogenase (PDH) and pyruvate carboxylase, respectively (Fig. 1). PDH is an important site of regulation, being activated by an elevation of mitochondrial $[Ca^{2+}]$ [30,31]. PDH is also regulated by reversible phosphorylation of its E1α subunit, activity of the PDH kinases inhibiting the enzyme [32]. However, knockdown of both PDH kinase 1 and kinase 3 in INS-1E β-cells does not affect metabolism–secretion coupling [33].

Condensation of the acetyl group carried by Coenzyme-A with oxaloacetate yields citrate, thereby activating the tricarboxylic acid (TCA) cycle. The pyruvate carboxylase enzyme ensures the provision of carbon skeleton (i.e. anaplerosis) to the TCA cycle, a key pathway in β-cells [34]. The remarkably high anaplerotic activity in β-cells indicates important loss of TCA cycle intermediates (i.e. cataplerosis), which is compensated for by de novo oxaloacetate synthesis by pyruvate carboxylation. In the control of glucose-stimulated insulin secretion, TCA cycle intermediates are recruited to serve as substrates leading to the formation of mitochondrion-derived coupling factors [7].

The TCA cycle extracts reducing equivalents from its metabolic intermediates, which are then carried by NADH and $FADH_2$. In order to maintain input of pyruvate products into the TCA cycle upon glucose stimulation, such reduced redox state requires continued reoxidation of mitochondrial NADH to NAD^+, primarily by complex I of the electron transport chain. However, as complex I activity is thermodynamically limited, excess of NADH contributed by the high TCA cycle activity must be reoxidized by alternative dehydrogenases, notably by glutamate dehydrogenase [35] (see Fig. 1).

TCA cycle activation induces transfer of reducing equivalents to the electron transport chain resulting in hyperpolarization of the mitochondrial membrane, O_2 consumption, and generation of ATP (Fig. 1). ATP is then translocated to the cytosolic compartment in exchange for ADP by the adenine nucleotide translocator (ANT).

3.2. Activation of mitochondria by Ca^{2+}

Mitochondrial activity can be modulated by Ca^{2+} concentrations ($[Ca^{2+}]_m$) [30,36], mitochondrial protein tyrosine phosphatase [37], mitochondrial GTP [38], and matrix alkalinisation [39]. Among these factors, effects of $[Ca^{2+}]_m$ have attracted much attention. Elevation of $[Ca^{2+}]_m$ enhances mitochondrial oxidative activity [40] and promotes generation of coupling factors for insulin exocytosis [41]. Conversely, buffering mitochondrial free Ca^{2+} limits $[Ca^{2+}]_m$ peaks induced by glucose stimulation in INS-1E β-cells with corresponding effects on insulin secretion [42].

Regarding Ca^{2+} transport, the mitochondrial Ca^{2+} uniporter (MCU) has been identified as the channel responsible for mitochondrial Ca^{2+} uptake [43,44]. MCU is part of a complex located in the inner mitochondrial membrane and its activity is modulated by another protein, the mitochondrial Ca^{2+} uptake 1 (MICU1). MICU1 holds two Ca^{2+}-sensing EF hands, which are essential for its activity [45]. Silencing of MCU in insulin-secreting cells impairs the rise in $[Ca^{2+}]_m$ evoked by cell depolarization and reduces both O_2 consumption and ATP rise upon glucose stimulation [46,47]. Accordingly, knockdown of MCU in rodent β-cells inhibits glucose-induced exocytosis [46,47]. Similarly, silencing of MICU1 in insulinoma cells reduces mitochondrial Ca^{2+} uptake, ATP levels, and insulin secretion upon glucose stimulation [48]. Mitochondrial Ca^{2+} efflux is mediated by the Na^{2+}/Ca^{2+} exchanger (NCLX) [49]. In pancreatic β-cells, silencing of NCLX extends elevations of $[Ca^{2+}]_m$ evoked by cell depolarization and accelerates the rise in ATP/ADP ratio in response to glucose stimulation [46]. Consistently, the rise in $[Ca^{2+}]_m$ evoked by glucose is enhanced in β-cells when NCLX is expressed in a dominant negative form [50], in agreement with CGP37157-mediated inhibition of the Na^{2+}/Ca^{2+} exchanger [51].

Collectively, these data indicate that both the channel and its regulatory partner, i.e. MCU and MICU1 respectively, are necessary for proper regulation of $[Ca^{2+}]_m$ in β-cells and participate in glucose-stimulated insulin secretion.

4. Mitochondria generate signals for insulin exocytosis

4.1. Coupling factors produced by mitochondria

Glucose metabolism induces both the triggering and the amplifying pathways, i.e. the necessary Ca^{2+} rise and the generation of additional coupling factors, respectively [6]. The amplifying pathway has been originally uncovered by glucose stimulation whilst maintaining cytosolic $[Ca^{2+}]$ clamped at permissive levels [52]. This suggested the existence of metabolic coupling factors, generated by glucose, participating in the amplifying pathway. Mitochondria have been identified as a source of additional coupling factors for insulin exocytosis. For instance, the demonstration has been done using permeabilized insulin-secreting cells clamped at permissive Ca^{2+} concentrations and simultaneously stimulated with mitochondrial substrates [41].

4.2. Nucleotides derived from mitochondria

ATP is the primary factor produced by mitochondria during glucose-stimulated insulin secretion (Fig. 1). Following its export in the cytosolic compartment through the exchanger ANT, ATP closes the K_{ATP}-channel leading to the obligatory Ca^{2+} elevation promoting insulin release [53]. Moreover, ATP is implicated in secretory granule movement [54,55] and their priming prior to exocytosis [56]. ATP also serves as a substrate for adenylyl cyclase at the plasma membrane for generation of the second messenger cAMP, which robustly potentiates glucose-stimulated insulin secretion [57]. Glucagon and GLP-1 (glucagon-like peptide 1) increase cAMP concentrations in β-cells [58], resulting in the amplification of the secretory response [59]. Of note, cAMP levels are negatively modulated by superoxide, an effect mediated by NADPH oxidases [60]. In particular, the glucose response of islets deficient in NOX2 is characterized by lower superoxide, higher cAMP levels, and increased insulin secretion [60].

NADH and its phosphorylated form NADPH are primarily responsible for transfer of reducing equivalents, NADPH being mainly localized in the cytosolic compartment. Glucose stimulation raises the NAD(P)H/$NAD(P)^+$ ratio [61], first in the cytosol and then in the mitochondria [62], before elevation in cytosolic $[Ca^{2+}]$ [63]. Glucose stimulation also increases the total pool of NADPH through the phosphorylating activity of NAD-kinase [64].

Cytosolic NADPH can be produced by glucose metabolism via the pentose phosphate shunt [65]. However, in β-cells an important role in the provision of NADPH is played by mitochondrial shuttles [66], in particular the pyruvate/citrate shuttle (Fig. 2A). The export of citrate out of the mitochondria might serve as a signal of fuel abundance, participating in metabolism–secretion coupling [66]. Once in the cytosolic compartment, citrate metabolism contributes to the formation of NADPH and acetyl-CoA (Fig. 2A), the latter being a substrate for malonyl-CoA and then long-chain acyl-CoA formation.

NADPH has been originally proposed as a coupling factor in glucose-stimulated insulin secretion using toadfish islets [67], showing a direct effect of NADPH on the release of insulin [68]. These effects were further substantiated in rodent β-cells, demonstrating direct stimulation of insulin exocytosis upon intracellular addition of NADPH [69].

4.3. Mitochondria as a source of precursors for fatty acids serving as coupling factors

In the cytosolic compartment, NADPH is also used for the synthesis of fatty acids. Upon glucose stimulation, citrate derived from mitochondria, generates cytosolic acetyl-CoA necessary for the synthesis of malonyl-CoA and then long-chain acyl-CoA (Fig. 2A). The malonyl-CoA thus formed lower fatty acid oxidation by inhibiting LCPTI (liver carnitine palmitoyltransferase), the rate-limiting step for transport and oxidation of fatty acids in mitochondria. Inhibition of fatty acid oxidation by malonyl-CoA increases the availability of lipid signals [70], thereby promoting the accumulation of long-chain acyl-CoAs [71,72], in turn enhancing Ca^{2+}-evoked insulin exocytosis [73]. Accordingly,

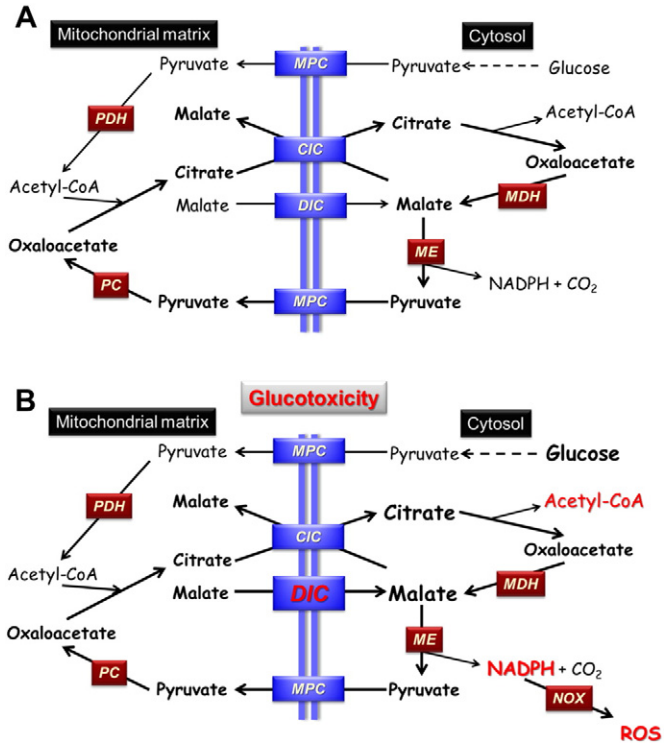

Fig. 2. The pyruvate/citrate shuttle and its adaptation to glucotoxicity. (A) Mitochondrial citrate is exchanged for cytosolic malate through CIC. In the cytosol, citrate forms acetyl-CoA and oxaloacetate, the latter producing malate by the malate dehydrogenase (MDH). Cytosolic malate can also be contributed by transport from mitochondria through DIC. Malic Enzyme (ME) produces pyruvate and NADPH. Pyruvate is then imported into mitochondria through MPC and the shuttle is completed by the actions of pyruvate carboxylase (PC) and regeneration of mitochondrial citrate. NADPH is a substrate for de novo fatty acid synthesis along with acetyl-CoA, as well as ROS-generating enzyme NADPH oxidase (NOX). (B) In glucotoxic conditions, upregulation of DIC favours export of malate, promoting export of citrate and the provision of cytosolic acetyl-CoA and NADPH. These are substrates for production of lipids and ROS.

LCPTI overexpression in INS-1E β-cells increases oxidation of fatty acids, whilst it reduces glucose-stimulated insulin secretion [74]. Fatty acids derived from triglyceride stores may also play a permissive role in the secretory response [75].

4.4. Mitochondrial glutamate as a coupling factor

Upon glucose stimulation, saturating levels of mitochondrial acetyl-CoA and NADH promote cataplerosis, i.e. leak out of TCA cycle intermediates [76]. Beside citrate [66], glutamate is an important cataplerotic product, allowing the necessary reoxidation of NADH to NAD^+ through the activity of glutamate dehydrogenase (GDH) [35].

The original finding that mitochondrial activation in permeabilized β-cells directly stimulates insulin exocytosis [41] initiated investigations that led to the identification of glutamate as a putative intracellular messenger [77–79]. Similarly to the role of fatty acids discussed above, work from our laboratory and others indicate that permissive levels of glutamate within the β-cell are necessary for the full development of glucose-stimulated insulin secretion. Abrogation of the glutamate rise upon glucose stimulation in GDH-null β-cells of β*Glud1*$^{-/-}$ mice prevents full development of the secretory response [80], in particular manifestation of the amplifying pathway [35]. This reduced secretory response is restored by provision of exogenous glutamate to the intracellular space [35]. Not only synthesis of glutamate is required upon glucose stimulation for the full development of the secretory response, but also its transport from the mitochondrial matrix to the cytosolic compartment (Fig. 1). This task is fulfilled by the glutamate carrier GC1, which silencing reduces insulin exocytosis evoked by glucose stimulation [81].

Downstream of mitochondria, glutamate would be taken up by secretory granules, thereby enhancing Ca^{2+}-dependent exocytosis [77,78]. Accordingly, insulin-secreting cells express vesicular glutamate transporters, allowing glutamate transport similarly to neurons [82]. Moreover, β-cells express both VGLUT3 and the excitatory amino acid transporter EAAT2 on insulin-containing secretory vesicles, favouring respectively import and export of glutamate [83]. Interestingly, a link has been established between glutamate and cAMP, a strong GLP1-dependent enhancer of insulin secretion described above. Indeed, glutamate uptake into insulin granules is mediated by cAMP/PKA, showing that glutamate acts as a key signal linking glucose metabolism and incretin/cAMP action to amplify insulin secretion [84] (see Fig. 1). Recently, delineation of a new pathway for amplification of insulin exocytosis has been described via sentrin/SUMO-specific protease-1 (SENP1), relying on the provision of cytosolic glutathione secondary to glucose-induced elevations of glutamate and NADPH [85]. Collectively, data point to a model for necessary permissive levels of intracellular glutamate rendering insulin granules exocytosis-competent.

Beside its intracellular effects, a new role has been recently uncovered for glutamate as an extracellular islet messenger reducing glucose-stimulated insulin secretion through activation of NMDA receptors on the β-cell [86].Thus, inside the cell glutamate taken up by secretory granules would enhance insulin secretion and then, once released out of the cell, glutamate would play a role as a negative feedback loop through glutamate receptors on the β-cell [87].

5. Metabolic stresses induce diabetogenic changes in mitochondrial carriers of β-cells

5.1. Glucolipotoxicity in type 2 diabetes

In most type 2 diabetes, hyperglycaemia appears as a result of significant loss of functional β-cells secondary to the exposure to a pathophysiological environment, commonly referred to as glucolipotoxicity [8,88–92]. However, little is known on mitochondrial responses and long-term adaptation to chronic exposure of β-cells to metabolic stresses; i.e. high glucose, fatty acids either saturated or unsaturated, and

oxidative stress. The respective contribution of the different components of the diabetogenic milieus to the dysfunction, dedifferentiation and ultimately death of the β-cell remains unclear; driven by changes in gene expression. We recently reported the specificities of mitochondrial targets to different metabolic stresses investigated individually side by side on β-cells. In these studies, INS-1E β-cells [93] and human islets [94] were chronically exposed to high glucose (25 mM), palmitate (saturated fatty acid), oleate (unsaturated fatty acid), and transient oxidative stress (H_2O_2 for 10 min). The resulting transcriptome of respiratory chain subunits and inner membrane carriers of the *Slc25* family is summarized in Fig. 3. It reveals that, following chronic exposure to diabetogenic milieus, INS-1E β-cells (Fig. 3A) and human islets (Fig. 3B)

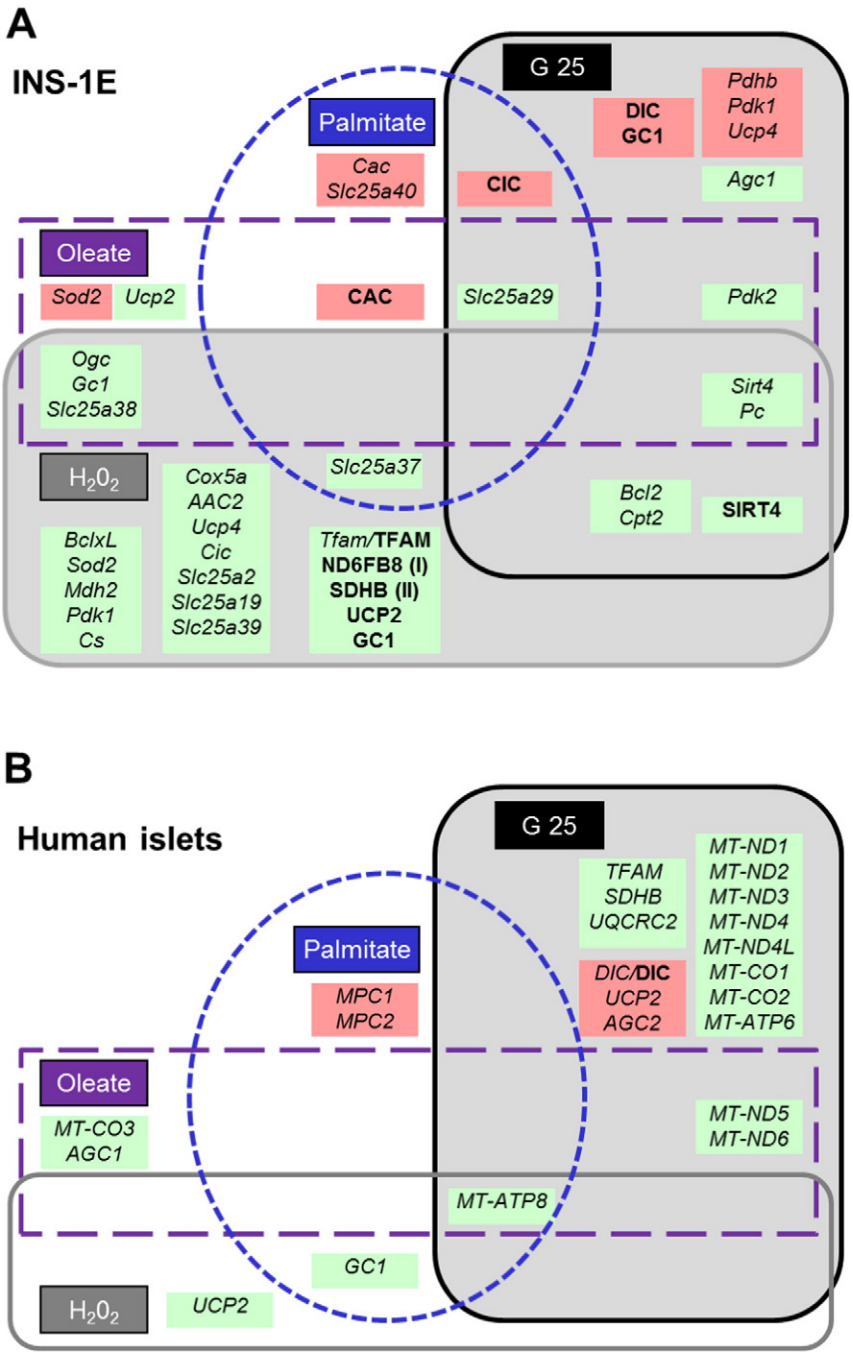

Fig. 3. Stress-specific mitochondrial transcriptome of INS-1E β-cells and human islets after chronic exposure to diabetogenic milieus. Changes in gene expression in (A) INS-1E β-cells and (B) human islets induced by the different metabolic stresses. Cells were exposed for 3 days to different culture conditions: 25 mM glucose (G25), 0.4 mM palmitate (Palmitate), 0.4 mM oleate (Oleate) and transient oxidative stress at day 0 (200 μM H2O2 for 10 min). Culture at standard 11.1 mM glucose (G11 for INS-1E cells) or at physiological 5.6 mM glucose (G5.6 for human islets) served as no-stress control. Italic names represent transcripts and capital bold letters represent proteins. Colours reflect changes in mRNA or proteins levels versus corresponding controls (green down <0.8, red up >1.2). Diabetogenic milieus where changes in gene expression were associated with significant cytotoxic effects are shown in grey. Adapted from [93,94]. Quantification of mitochondrion-associated gene trancripts includes: antiapoptotic genes, BclxL, Bcl2; antioxidative enzyme, SOD2 (superoxide dismutase); redox state-related sirtuin, Sirt4; mitochondrial enzymes Mdh2 (malate dehydrogenase), Pc/PC (pyruvate carboxylase), Pdhb (pyruvate dehydrogenase subunit beta), Pdk1, Pdk2 (pyruvate dehydrogenase kinase 1 and 2) Cs (citrate synthase), Cpt1a, Cpt2 (carnitine O-palmitoyltransferase); nuclear-encoded subunits of the five OXPHOS complexes: ND6FB8 (complex I), SDHB (complex II), UQCRC2 (complex III), Cox5a (complex IV), ATP5C1 (complex V); mtDNA-encoded (MT) subunits, NADH dehydrogenase ND1-ND6 (complex I), ubiquinol:cytochrome c oxidoreductase CYB (complex III), cytochrome c oxidase CO1–CO3 (complex IV), ATP synthase ATP6 and ATP8 (complex V); metabolite carriers, pyruvate MPC1 and MPC2, citrate/isocitrate Cic/CIC, malate Dic/DIC, 2-oxoglutarate/malate Ogc/OGC, aspartate/glutamate Agc1/AGC2, Agc2/AGC2, glutamate Gc1/GC1, malate/oxaloacetate/aspartate Ucp2/UCP2, uncoupling protein Ucp4; carnitine/acylcarnitine carrier Cac.

Table 2
Overview of alterations in INS-1E β-cells and human islets induced by the different metabolic stresses. Global view of the expression of the mitochondrial inner membrane carriers, respiratory chain subunits and energy sensors after stress exposure. Culture at standard 11.1 mM glucose (G11 for INS-1E cells) or at physiological 5.6 mM glucose (G5.6 for human islets) served as no-stress control. Colours reflect changes in mRNA or proteins levels versus corresponding controls (green down <0.8, red up >1.2, grey no change, white not tested).

			G 25		Palmitate		Oleate		H_2O_2	
Gene symbol	Name		INS–1E β–cells	Hum. islets	INS–1E β–cells	Hum. islets	INS–1E β–cells	Hum. islets	INS–1E β–cells	Hum. islets
BRP44l / BRP44	MPC1 / MPC2	mRNA	–		–		–		–	
		Protein	–	–	–	–	–	–	–	–
SLC25 A1	CIC	mRNA								
		Protein								
SLC25 A10	DIC	mRNA								
		Protein								
SLC25 A11	OGC	mRNA								
		Protein	–	–	–	–	–	–	–	–
SLC25 A8	UCP2	mRNA								
		Protein		–		–		–		–
SLC25 A12	AGC1	mRNA								
		Protein		–		–		–		–
SLC25 A13	AGC2	mRNA								
		Protein		–		–		–		–
SLC25 A22	GC1	mRNA								
		Protein		–		–		–		–
SLC25 A20	CAC	mRNA		–		–		–		–
		Protein								
OXPHOS subunits (I)	MT–ND	mRNA	–	MT–ND1–6	–		–	MT–ND5/6	–	
	ND6FB8	Protein								
OXPHOS subunits (II)	SDHB	mRNA	–		–		–		–	
		Protein								
OXPHOS subunits (III)	UQCRC2	mRNA	–		–		–		–	
		Protein								
OXPHOS subunits (IV)	MT–CO	mRNA		MT–CO1/2				MT–CO3	Cox5a	
	COX1	Protein								
OXPHOS	MT–ATP	mRNA	–	MT–ATP6/8	–	MT–ATP8	–	MT–ATP8	–	MT–ATP8
subunits	ATP5A1	Protein								
TFAM	TFAM	mRNA								
		Protein								
SIRT4	SIRT4	mRNA		–		–		–		–
		Protein								

exhibit stress-specific signatures. Of note, the reported stress-responses were observed on intact pancreatic islets, being by essence composed of different cell types, insulin-secreting β-cells composing the major fraction of such micro-organ [1]. Correspondence with unmixed fraction of insulin-secreting cells, INS-1E β-cells, is displayed in Table 2, confirming a good correlation between this rat cell line and human islets when exposed to diabetogenic milieus [95]. However, the respective contribution of each human islet cell type to the stress-response remains to be delineated.

5.2. Mitochondrial markers of oxidative stress

As shown in Fig. 3A, one single transient oxidative stress applied to INS-1E β-cells and rat islets markedly alters the expression of genes required for mitochondrial metabolism and impairs β-cell function and survival over days [93,96,97]. Human islets, on the contrary, are more resistant to oxidative attack and exhibit preserved glucose-stimulated insulin secretion and no significant cell death [94]. Interestingly, human transcript levels of the β-cell specific transcription factor *MAFA* [98] and the C5 and C4 mitochondrial carriers *GC1* and *UCP2* are down-regulated following oxidative stress [94], similarly to INS-1E β-cells [93], conferring to these targets a stress-specific signature (Fig. 3 and Table 2).

5.3. Mitochondrial markers of saturated and unsaturated fatty acids

Rat and human islets exposed for a short time to palmitate and oleate increase their basal insulin release and fail to respond to stimulatory glucose [99–101]. Regarding chronic exposure, the notion of lipid-induced toxicity, or lipotoxicity, in type 2 diabetes was first proposed in the mid-nineties [102]. Such β-cell dysfunction, induced for instance by palmitate or oleate, is usually not associated with cytotoxic effects, pending concomitant exposure to physiological glucose concentrations, at least in INS-1E β-cells and human islets [93,94]. Thus, the lipodysfunction developed by isolated human islets is similar to what is observed in rat islets and INS-1E β-cells [103], and in accordance with the effects of circulating free fatty acids reported in islets from patients with type 2 diabetes [104]. Selective lipid exposure of the β-cells uncovered mitochondrial targets specifically associated with the nature of the fatty acids (Fig. 3). Both saturated and unsaturated fatty acids increase expression of the carnitine/acylcarnitine carrier CAC, whereas palmitate specifically increases expression of the citrate carrier CIC in INS-1E β-cells (Fig. 3A). In human islets (Fig. 3B), the pyruvate carriers MPC1 and MPC2 are upregulated by palmitate, whereas the glutamate carrier GC1 and the aspartate/glutamate carrier AGC1 are selectively down-regulated by palmitate and oleate, respectively, showing fatty acid-specific responses. Palmitate also represses expression of genes involved in ATP production, including citrate synthase and mitochondrial ATP synthase [94,100], possibly contributing to the loss of glucose-stimulated insulin secretion. Overall, chronic exposure of β-cells to palmitate and oleate induces limited but lipid-specific changes in expression of genes of the mitochondrial machinery (Table 2).

5.4. Delineation of mitochondrial markers of glucotoxicity

Hyperglycaemia is associated with β-cell dedifferentiation, altered glucose-stimulated insulin secretion and increased cell death [14,88,90,105]. A progressive deterioration and loss of β-cells is observed in patients with type 2 diabetes [8,9]. Studied in vitro, chronic exposure to high glucose markedly impairs glucose-stimulated insulin secretion, decreases insulin content, and promotes caspase-3 cleavage and cell death in INS-1E β-cells [93] and human islets [94]. Such deleterious effects are referred to as glucotoxicity [106].

Fig. 3 and Table 2 show the expression of key mitochondrial components being changed by chronic high glucose. High glucose down-regulates energy-sensors *Sirt1*/SIRT1 and *Sirt4*, as well as key transcription factors (*Pdx1*/*IPF1*, *Ppara*/*PPARA*). SIRT1 activity depends on NAD^+/NADH ratio and consequently serves as a redox energy sensor acting as a transcriptional activator via deacetylase activity. In β-cells, the main SIRT1 targets are HNF-1α and *IPF1* [107]. Pdx1/IPF1 is a master regulator of genes implicated in β-cell development and function [91,108,109]; such as the glucose transporter *GLUT2*, the glucose sensor glucokinase *GCK* and insulin. Expression of the mitochondrial transcription factor TFAM, involved in the maintenance and transcription of mtDNA, is reduced in human islets exposed to high glucose [94]. Of note, Tfam is a direct target of Pdx1 that binds to its promoter [110]. In rat islets, defective Pdx1 down-regulates *Tfam* and *mt-Nd1*, along with reduced mtDNA content and altered mitochondrial activity [110,111]. Consistently, high glucose reduces expression of nuclear-encoded respiratory chain subunits II (*SDHB*) and III (*UQCRC2*) in islets. A striking effect of glucotoxicity on human islets is the global down-regulation of 11 mtDNA-encoded respiratory chain subunits (Fig. 3B).

Recently, Pdx1 was also demonstrated to regulate mitophagy in β-cells. Mitophagy mediates quality control of mitochondria and preserves cellular respiration by eliminating dysfunctional mitochondria [14,112,113]. In *Pdx1*$^{+/-}$ islets, Pdx1 deficiency reduces mtDNA content, alters mitochondrial ultrastructure, and impairs fusion of autophagosomes containing mitochondria to lysosomes; resulting in β-cell dysfunction [114]. Loss of Pdx1 decreases expression levels of *Clec16a*, a type 1 diabetes-associated gene and a key mediator of mitophagy [115]. Overexpression of *Clec16a* restores mitochondrial morphology and mitophagy, improves mitochondrial respiration and insulin secretion, without re-establishing mtDNA content [114]. Thus, Pdx1 orchestrates nuclear control of mitochondrial function by regulating both mtDNA-encoded respiratory chain subunits through TFAM and mitophagy through Clec16a. However the specific effects of glucotoxicity on mitophagy remain to be uncovered.

Taken together, data suggest interdependence between transcription regulators, where chronic high glucose would primarily decrease expression of *SIRT1* and *IPF1*, in turn down-regulating *TFAM* and mtDNA-encoded respiratory chain subunits (Fig. 3). Consequently, this may alter mitochondrial ATP production and glucose-stimulated insulin secretion. In the long run, impaired electron transport chain activity secondary to repressed mitochondrial gene expression may lead to increased susceptibility of β-cells to apoptosis.

Insulin secretion is triggered and maintained via integration and production of signals by the mitochondria [7,116]. In particular, pyruvate couples glycolysis to mitochondria, fueling the TCA cycle and resulting in the generation of metabolic signals, such as ATP or glutamate (Fig. 1). Chronic high glucose modifies neither *MPC1* nor *MPC2* expression in human islets [94], indicating that pyruvate transport is preserved in these conditions. On the contrary, glucotoxicity up-regulates INS-1E mitochondrial carriers CIC (citrate) and GC1 (glutamate), as well as DIC (malate) and AGC2 (aspartate/glutamate) in human islets (Fig. 3). Such profile suggests important mitochondrial anaplerotic/cataplerotic and NADPH-generating shuttle activities induced by high glucose (Fig. 2B). The associated decrease of respiratory chain subunits favours saturation of the electron transport chain, promoting citrate export through CIC and consequently provision of cytosolic acetyl-CoA and de novo lipid synthesis, an effect substantiated by the observed increase of lipogenic enzyme acetyl-CoA carboxylase ACC [94]. Regarding fatty acid synthesis upon chronic high glucose, increased citrate export out of the mitochondria through CIC requires an enlarged pool of cytosolic malate (Fig. 2A). Indeed, CIC exchanges mitochondrial citrate for cytosolic malate, the latter being produced from citrate-derived oxaloacetate in the cytosol. In glucotoxic conditions, provision of additional cytosolic malate can be achieved by transport through DIC (Fig. 2B), which is up-regulated by high glucose (Table 2).

Another observation is the glucose-dependent up-regulation of UCP2 in human islets (Fig. 3B). UCP2 has been implicated in numerous physiopathological conditions, including hyperglycaemia and diabetes [14,90]. It was originally suggested that effects of UCP2 were mediated

by mitochondrial uncoupling activity, regulating ROS production. However, the recent demonstration of C4-metabolite transport properties of UCP2 shed a new light on the role of UCP2 upon hyperglycaemia [117] (see Table 1). Increasing mitochondrial export capacity of the C4-metabolites oxaloacetate and malate through both AGC1/2 and UCP2 up-regulation would reduce TCA cycle activity, thereby lowering the redox pressure and ATP production. The mitochondrial redox pressure is also contributed by NADH shuttles, having redundant routes in β-cells [118], AGC1/2 being implicated in the malate–aspartate shuttle [24,25]. Up-regulation of AGC2 upon glucotoxicity (Fig. 3B) could increase the capacity of aerobic glycolysis in islets.

A key feature of glucotoxicity is the up-regulation of the mitochondrial malate carrier DIC, as observed in INS-1E β-cells [93], rat islets [119], and human islets [94]. DIC is a critical shuttle component for cytosolic NADPH production mediated by pyruvate cycling [120,121]. In neurons, DIC mediates glutathione transport and the mitochondrial GSH pool, which participates in ROS homeostasis [122]. In β-cells, the NADPH oxidase NOX2 negatively modulates glucose-stimulated insulin secretion by promoting ROS generation and reducing cAMP [60]. Accordingly, up-regulation of DIC upon high glucose could promote generation of ROS in the cytosolic compartment, in turn inhibiting insulin release (Fig. 2B).

Overall, Fig. 3 and Table 2 summarize the specific changes induced by glucotoxicity on the expression profile of mitochondrial energy sensors, respiratory chain subunits and mitochondrial carriers, delineating a glucotoxic-specific signature.

6. Conclusions

In pancreatic β-cells, mitochondrial carriers play a central role in the coupling of glucose metabolism with the exocytotic machinery. Mitochondria translate glucose levels into signals controlling the rate of insulin exocytosis. This requires transport of molecules in and out of the mitochondria. In conditions of pre-diabetes, chronic elevation of circulating free fatty acids and frequent episodes of hyperglycaemia promote alterations of the β-cell, potentially leading to β-cell death. Recent reports have shown that glucolipotoxicity induces early changes in the expression of mitochondrial components, in particular of metabolite carriers. Upon glucotoxic conditions, up-regulation of a selection of mitochondrial carriers (CIC, GC1, UCP2, AGC2 and DIC), which favour export of metabolites out of the mitochondria, may lower the catabolic pressure of glucose on mitochondrial oxidative activity, suggesting a mitohormetic response [123]. Regarding potential drug treatments, reducing mitochondrial import of the glucose product pyruvate by inhibiting MPC could be beneficial for type 2 diabetic patients. Indeed, thiazolidinediones, which are widely used for treatment of type 2 diabetes, have recently been shown to inhibit MPC [124]. Recent advances in the characterization of mitochondrial carriers may pave the way for new treatments of type 2 diabetes, targeting mitochondrial function.

Transparency document

The Transparency document associated with this article can be found, in online version.

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