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THE STRUCTURE AND FUNCTION OF MITOCHONDRIA-ASSOCIATED ENDOPLASMIC RETICULUM MEMBRANES AND THEIR ROLE IN PANCREATIC β-CELLS DYSREGULATION

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Membrane trafficking and organelle contact sites are important for regulating cell metabolism and survival. The highly specialized regions of close contacts between mitochondria and endoplasmic reticulum (ER), called mitochondria associated membranes (MAMs), are crucial signaling hubs for the lipid and calcium homeostasis, reactive oxygen species delivery, regulation of autophagy and mitochondrial dynamics. In recent years, MAMs have been the focus of multiple studies for identifying the MAMs proteins and defining their signaling mechanisms. Many studies have proved the importance of MAMs in maintaining the normal function of both organelles. Excessive MAM formation is known to trigger the cascade of pathological events, such as mitochondria calcium overload, aberrant lipid levels, autophagosome formation, and eventually, cell apoptosis. In this article, we focus on the composition and function of MAMs, more specifically, the role of MAMs in Ca^{2+} uptake, ER stress, mitochondrial fusion and fission and autophagy. The altered interaction between ER and mitochondria results in the amendment of pancreatic tissues, revealing the role of MAMs in glucose homeostasis and the development of diabetes. The development of mitochondrial dysfunction, ER stress and oxidative stress are co-related with β-cell dysfunction. MAMs are likely to play an important role of the functional state regulation in pancreatic cells under pathologies by regulating the signaling of the two organelles and the crosstalk of the two pathological events. It was found that under streptozotocin-induced diabetes, the increased level of mitophagy in pancreatic tissue is connected with tight junctions of MAMs.

Keywords: mitochondria, endoplasmic reticulum, MAMs, ER stress, mitophagy

ABBREVIATIONS:

ER – endoplasmic reticulum
UPR – unfolded protein response
MAMs – mitochondrial-associated ER membranes
OMM – outer mitochondrial membrane
IP3R – inositol 1,4,5-triphosphate receptor
Sigma1R – sigma non-opioid intracellular receptor 1
VDAC – voltage-dependent anion-selective channel of mitochondrial OMM
GRP75 – glucose-regulated protein 75
VAPB – vesicle-associated membrane protein-associated protein B
PTPIP51 – protein tyrosine phosphatase interacting protein-51
Bap31 – B-cell receptor-associated protein 31
Fis1 – mitochondrial fission protein 1
IMM – inner mitochondrial membrane
ROS – reactive oxygen species
mPTP – mitochondrial permeability transition pore
MCU – mitochondrial Ca^{2+} uniporter
IP3 – inositol 1,4,5-trisphosphate
AXER – ATP/ADP exchanger in the ER membrane
Akt – protein kinase B
mTORC2 – mammalian TOR complex 2
SERCA – sarcoplasmic/endoplasmic reticulum $Ca(^{2+})$
Drp1 – dynamin-related protein 1
INF2 – inverted formin 2
MITOL – mitochondrial ubiquitin ligase
Mfn1/2 – Mitofusin 1 or 2
MTCH2 – mitochondrial carrier 2
OPA1 – mitochondrial dynamin like GTPase
PERK – protein kinase-like ER kinase
IRE1α – inositol requiring enzyme 1
ATF6 – activation transcription factor 6
ULK – unc-51-like autophagy-activating kinase
XBP1 – box binding protein 1
PINK1 – PTEN-induced putative kinase 1

The endoplasmic reticulum (ER) is the key coordinator of the cell's response to metabolic modulation and changes its morphology in response to the cell's specialised function and metabolic status. It maintains nutrient homeostasis, protein synthesis and folding, glucose metabolism, calcium signaling, lipid synthesis and lipid droplet biogenesis. The ER has evolved several pathways to adapt to stress and metabolic changes which include activation of the unfolded protein response (UPR), ER volume expansion, sensing cholesterol concentrations, and remodeling its contact network with other organelles (Achleitner *et al.,*1999). When the ER senses stress, a change in energy demand or the cellular metabolism, an adaptive change in morphology of the ER and its membrane interaction interfaces with other organelles will occur to maintain cellular homeostasis. Different specialized areas of the ER are shown to be enriched in specific factors and involved in regulating different ER functions. Membrane contact sites

formed by the ER are necessary to facilitate communication between organelles and the transport of ions and lipids across membranes. Among these, the mitochondrial-associated ER membranes (MAMs) are transient domains in the ER in close apposition to mitochondria. Mitochondria form two types of ER contact sites: first, those that are juxtaposed to the smooth ER (MAMs) and second, those that contact the rough ER – wrappER-associated mitochondria (WAMs). The WAMs regulate the biogenesis of very-low-density-lipoproteins in the liver and whole-body lipid homeostasis (Gelmetti *et al.,* 2017). The MAMs are important structures for regulation of intracellular lipid metabolism, lipid synthesis, calcium signaling, mitochondrial function and apoptosis (Achleitner *et al.,* 1999). Recent research has shown an important role of membrane contact between the ER and mitochondria in a number of diseases, including inflammation, neurodegenerative disorders, cancer and obesity. In the 1950s, electron microscopy captured the first interorganellar contacts between the ER and the mitochondria, but they were dismissed by many as an artifact (Yuan *et al.,* 2020) until the MAMs were first isolated from a crude rat liver mitochondrial preparation in the laboratory of Dr. Vance in 1990 (Bai *et al.,* 2019). Later it was found that as much as 20 % of the mitochondria are juxtaposed to the ER in HeLa cells (Delprat *et al.,* 2020). Like mitochondria themselves, the MAMs are dynamic and often occur only transiently. Electron tomography images revealed that ER and mitochondria are linked by tethers formed from specific protein–protein interactions. Overlapping apposition distances between the ER and outer mitochondrial membrane (OMM) vary approximately between 10 and 50 nm across from smooth ER. For rough ER with attached ribosomes this distance is greater – 50–80 nm (Vance *et al.,* 1999). Biophysically, the MAMs have the characteristics of a lipid raft, which are membrane domains rich in cholesterol and sphingomyelin that act as temporary signaling platforms or hubs, involved in the regulation of different metabolic processes. As a lipid raft, when formed, it induces the recruitment of specific proteins involved in the regulation of cholesterol metabolism, synthesis and acylation of phospholipids and taking calcium homeostasis such as ER inositol 1,4,5-triphosphate receptor (IP3R), sigma non-opioid intracellular receptor 1 (Sigma1R), voltage-dependent anion-selective channel of mitochondrial OMM (VDAC) and ER stromal interaction molecule 1.

Within yeast, there are an estimated ~ 110 ER–mitochondrial contacts at baseline (Means *et al.,* 2022). However, the number of MAMs increases during apoptosis (Degechisa *et al.,* 2022). Physiologically, the MAMs fluctuate dynamically to regulate cellular function, such as autophagy, mitochondrial dynamics, and lipid and calcium trafficking between the mitochondria and ER (Achleitner *et al.,*1999). These two organelles are tethered by several molecular components of the MAMs fraction. At least eight protein complexes have been identified at the MAM sites (Yang *et al.,*2020b). One of the most well-characterized macromolecular complexes of MAMs is complex IP3R and VDAC1, which are connected cytoplasmic chaperone glucose-regulated protein 75 (GRP75). This complex regulates ER-mitochondrial Ca^{2+} transfer (Li *et al.,* 2022). Another tethering complex, that consists of ER vesicle-associated membrane protein-associated protein B (VAPB) and mitochondrial membrane protein tyrosine phosphatase interacting protein-51 (PTPIP51), facilitates IP3R mediated delivery of Ca^{2+} from ER to mitochondria. Besides, this complex is involved in vesicle trafficking, UPR and tumorigenesis (Mórotz *et al.,* 2022, Yu *et al.,* 2008). The ER-localized B-cell receptor-associated protein 31 (Bap31) interacts with mitochondrial fission protein 1 (Fis1) by forming the Bap31–Fis1 MAMs complex (Iwasawa *et al.,* 2011), which involves in mitochondrial fission and apoptosis signaling.

Notably, excessive MAMs formation is known to trigger the cascade of pathological events, such as mitochondria calcium overload, abnormal lipid levels, autophagosome formation, and ultimately cell apoptosis (Yuan *et al.,* 2020). Indeed, disturbances in mitochondrial function have been largely associated with upregulated MAMs function, augmented cross-talk between these two organelles and increased expression of Ca^{2+} channels (IP3R and VDAC1) (Marinho *et al.,* 2023). However, the mechanisms underlying the induction of MAMs dysfunction by hyperglycemia in diabetes remain unknown.

Mitochondrial Ca^{2+} import. Calcium is a fundamental second messenger in the intracellular communication and plays pivotal roles in multiple cellular processes. A rapid change of cytosolic Ca^{2+} can transmit signals from extracellular or intracellular stimuli to corresponding effector molecules or organelles in cells (Parys and Guse, 2019). The ER is one of the major stores for Ca^{2+}, which is released via transmembrane channels from the ER to regulate intracellular Ca^{2+} concentration (Raffaello *et al.,* 2016). Once inside mitochondria, Ca^{2+} is used at low levels in a number of metabolic processes, including the stimulation of complex III, ATP synthase, and adenine nucleotide translocase and the activation of pyruvate, isocitrate, and α-ketoglutarate dehydrogenases (Cárdenas *et al.,* 2010). In addition, mitochondrial Ca^{2+} triggers K^+ and water influx into the mitochondrial matrix leading to the matrix volume increase and a subsequent release of hydrogen peoxide at the MAMs (Booth *et al.,* 2016). However, increased Ca^{2+} transfer supports continued growth of cancers by supplying Ca^{2+} at a level sufficient for basal respiration that maintains increased metabolism (Ueasilamongkol *et al.,* 2020). Likewise, mitochondrial Ca^{2+} uptake was found crucial for effective insulin signaling in skeletal muscle cells and cardiac myocytes (Degechisa *et al.,* 2020). However, mitochondrial Ca^{2+} levels require a delicate balance, as persistent increased amounts lead to cell death (Rizzuto *et al.,* 2012). Ca^{2+}-overload contributes to the oxidation of mitochondrial membrane lipids, in particular cardiolipin, a principal lipid in the inner mitochondrial membrane (IMM) that harbors the components of the respiratory chain, including complex II. This process promotes the disintegration of respiratory chain complex II, thus leading to the release of multiple subunits. This also induces the production of large amounts of reactive oxygen species (ROS) and mitochondrial permeability transition pore (mPTP) opening (Hwang *et al.,* 2014). This in turn causes IMM permeability, loss of mitochondrial membrane potential, mitochondrial swelling, OMM rupture, and necrosis (Means *et al.,* 2022). Ca^{2+} release in microdomains formed by intercompartmental contacts, such as MAMs is mediated by four major proteins which include IP3R, VDAC1, Grp75, and mitochondrial Ca^{2+} uniporter (MCU) reside in MAMs, OMM, cytosol, and IMM, respectively (Tessier *et al.,* 2023, Degechisa *et al.,* 2023).

IP3R are ER-resident, integral membrane proteins, which work as signaling hubs and is related to a series of regulatory molecules ranging from ions and proteins to small chemical compounds (Wright & Wojcikiewicz, 2016; Prole & Taylor, 2016). More importantly, IP3R is a tether protein that is involved in the formation of MAMs. IP3R channels are key elements of Ca^{2+} signaling machinery and reside in close proximity to the interface between ER and mitochondria microdomains to facilitate the transfer of Ca^{2+} ions (Gouriou *et al.,2023*).

There are three IP3R isoforms with 60–80% homology in mammalian cells (termed IP3R1, IP3R2, and IP3R3), which are different in sensitivity, regulation by Ca^{2+} and ATP, post-translational modification, localization to the MAMs, distribution in different tissues (Prole & Taylor, 2016). For channel opening, the second messenger inositol 1,4,5-trisphosphate (IP3) must bind to multiple IP3R subunits within the tetramer (Cárdenas

et al., 2010). Then IP3R relays signals by releasing Ca^{2+} from the ER lumen, which regulates numerous pathological and physiological processes including mitochondrial metabolism, neurotransmitter release, and the regulation of cell division and proliferation (Mikoshiba, 2015). Simulation modeling demonstrated that IP3R is synergistically activated in β-cells by glucose metabolism and the glucagon-like peptide-1–cAMP pathway (Takeda *et al.* 2016).

Alternatively, while IP3Rs maintain a 15 nm ER–mitochondrial separation, optimal for Ca^{2+} transfer, the presence of IP3Rs may create a nonoptimal distance for other signaling pathways, which may lead to their inhibition (Means *et al*., 2022). Mitochondrial Ca^{2+} uptake via MAMs leads to the activation of the tricarboxylic acid cycle and stimulates ATP syntheses. High luminal Ca^{2+} levels are also mandatory for maintaining a Ca^{2+} gradient across the ER membrane, which is required for ATP import (Daverkausen-Fischer *et al*., 2022). The MAMs were associated lately with the ATP transport into the ER *via* ATP/ADP exchanger in the ER membrane (AXER). High cytosolic Ca^{2+} concentrations (ranging between 500 nM and 2 μM) block AXER activity and inhibit ATP import into the ER through a Ca^{2+}-Antagonized Transport into ER (Lim *et al*., 2021).

It has been reported that IP3Rs directly interacts with VDAC1 located at the OMM. Ca^{2+} ions are taken across the OMM by VDAC, permeable to small cations in the closed state and respiratory substrates, ATP, and ROS in the open state. VDAC isoforms in mammals show differences in the mitochondrial localization: VDAC1 and VDAC2 are colocalized within the same restricted area in the OMM, while VDAC3 is widely distributed on the OMM (Reina *et al*., 2022). In contrast, VDAC2 inhibits apoptosis by binding pro-apoptotic effector protein BAK and VDAC3 does not appear to influence apoptosis. In pancreatic cells, an increased energy potential results in inhibition of K_{ATP} channels and activation of VDAC, which then triggers insulin release via elevated Ca^{2+}·(Doliba *et al*., 2007). Furthermore, the increased VDAC level in diabetic mouse endothelial cells is responsible for increased mitochondrial Ca^{2+} concentration, mitochondrial O_2^- production, and mPTP opening activity (an indirect indicator of cell apoptosis) (Sasaki *et al*., 2012). In contrast, depleting VDAC1 in pancreatic β-cells leads to enhanced ATP generation and the subsequent plasma membrane depolarization with increased cytosolic Ca^{2+} and insulin secretion, which protects β-cells against high glucose levels and maintains the reductive capacity of cells (Zhang *et al*., 2019).

GRP75 can connect the channel from the N-terminal of IP3R to VDAC1 and enhance Ca^{2+} transfer. IP3R3 is regulated by phosphorylation by protein kinase B (Akt) resulting in a decrease in Ca^{2+} release and cell death. Furthermore, mammalian TOR complex 2 (mTORC2) can phosphorylate Akt at the ER and ER stress inhibits mTORC2 activity, suggesting functional mTORC2-Akt signaling at the ER/MAMs (Betz *et al*., 2013). Unlike OMM, the IMM is not permeable for Ca^2 located in the intermembrane space. It is transferred to the mitochondrial matrix through MCU, which creates high Ca^{2+} microdomains necessary for Ca^{2+} transport. Also, receptor-interacting protein kinase 1 increases mitochondrial Ca^{2+} uptake and energy metabolism by binding to the MCU (Zeng *et al*., 2018).

Although Sigma1R is one of the two types of sigma receptors present in the ER membrane and at the MAMs, it has been found to translocate to other subcellular regions, such as the plasma membrane after stimulation by agonists (Couly *et al.,*2020), to regulate activity of various functional proteins, including ion channels, receptors and kinases (Su *et al.,*2010). When regulating Ca^{2+} at the MAMs, it forms a complex with

a major ER GRP75. When calcium levels are low or SigmaR1 is stimulated via ligand binding, SigmaR1 dissociates from the complex causing increased calcium signaling by IP3Rs, an ER-resident membrane protein, and thus acts as Ca^{2+}-sensitive chaperone, leading to apoptosis (Bai *et al.,*2019).

The sarcoplasmic/endoplasmic reticulum Ca($^{2+}$) ATPase (SERCA) localized in the ER membrane regulates $[Ca^{2+}]_{ER}$ levels, is also present in the MAMs. It has been reported that calnexin and thioredoxin-related transmembrane protein regulate SERCA2b activity through a direct interaction with SERCA2b in a palmitoylation-dependent manner (Yu *et al.,* 2021). Excessive $[Ca^{2+}]_{ER}$ release or a decreased activity of SERCA induces unfolded protein accumulation and ER stress in pancreatic β-cells, leading to defective insulin secretion and diabetes (Nguyen *et al.,* 2023).

Mitochondrial dynamics. Mitochondria are highly dynamic organelles. They can change their morphology to create a fragmented or tubular network and to move along the cytoskeleton with coordinated fission and fusion processes. These structural changes are key not only to the production of ATP, but also for the control of cell metabolism, autophagy, differentiation, immune responses, and cell death (Means *et al.,* 2023).

Mitochondrial fission is important for the correct distribution of mitochondria between daughter cells during division, as well as for autophagy, maintenance of energy balance, and in the intrinsic apoptosis pathway. The main enzyme accounting for fission is the dynamin-related protein 1 (Drp1). This GTPase located in the MAMs can regulate dynamic changes in mitochondria. Mechanistically, ER-localized inverted formin 2 (INF2) induces actin polymerization and recruits Drp1 in mitochondrial-ER contacts, triggering midzone division of mitochondria (Kleele *et al.,* 2021). Fission is negatively regulated by another actin-interacting protein, coffilin 1, that is required for local actin dynamics at mitochondria, where it may balance actin polymerization induced by INF2 and spire type actin nucleation factor 1C (Rehklau *et al.,* 2017). Thus, following constriction, some oligomerized Drp1 is transferred from the ER to the MAM-resident receptor proteins: mitochondrial fission factor, mitochondrial dynamic protein 49 and 51. Upon recruitment to the mitochondrial membrane, Drp1 forms helical oligomers in the OMM in a GTP-dependent manner which encircles, constricts, and cleaves the mitochondrion into two daughter mitochondria. The activity of Drp1 is modulated by post-translational modifications, including phosphorylation/dephosphorylation by glycogen synthase kinase 3 beta, Akt and protein kinase A located in the MAMs, and ubiquitination by glycoprotein 78, as well as other MAM-resident ligases, such as mitochondrial ubiquitin ligase (MITOL: also known as MARCH5) (Sugiura *et al.,* 2013). The impaired function of coronary endothelial cells in diabetic mice is correlated with an increased expression level of Drp1 (Joshi *et al.,* 2015). In addition, in diabetic cardiomyopathy models, increased Drp1 levels are associated with mitochondrial fragmentation, ROS accumulation, and endothelial cell apoptosis (Tao *et al.,* 2018).

Outer mitochondrial membrane fusion in mammalian cells is driven by two dynamin-related GTPases, Mitofusin 1 and 2 (Mfn1/2). These two proteins act both to shape mitochondrial membranes *in cis* to potentiate fusion and to act as “distance holder” within the two organelles while achieving the optimal distance between ER and mitochondria of 15–20 nm (Lim *et al.,* 2021). Mfn1 is exclusively located on the mitochondrial membrane, whereas Mfn2 is located on both the ER and mitochondrial membranes. The ratio of these proteins also dictates selection of the ER membrane, with higher Mfn1 interacting with rough ER and higher Mfn2 with smooth ER. Mfn2, due to ubiquitylation by

MITOL and increasing its GTPase activity, results in the tethering between the ER and mitochondria rather than mitochondrial fusion. Additionally, the loss of Mfn2 induces ER stress by disrupting the ER-mitochondria communication (de Brito and Scorrano, 2009). Importantly, Mfn1 and Mfn2 are critical regulators of the mitochondrial network in β-cells and consequently of insulin secretion *in vitro* and *in vivo* (Georgiadou *et al.,* 2022). The mitochondrial carrier 2 (MTCH2) has been reported to lead to mitochondrial fusion, as its loss in fibroblasts and embryonic stem cells results in mitochondrial fragmentation (Guna *et al.,* 2022). IMM fusion is not well studied, but involves the mitochondrial dynamin like GTPase (OPA1) and Mfn2-dependent pathway regulates an inactivating cleavage of OPA1, connecting to loss of cristae density and large increase of MAMs length. The assumption was made that the loss of the cristae could allow the IMM to distend and juxtapose under the MAMs to allow efficient calcium, lipid, and metabolite transfer across both mitochondrial membranes (Sood *et al.,* 2014).

ER stress. The accumulation of unfolded/misfolded proteins within the ER causes ER dysfunction (ER stress) (Chen *et al.,* 2023). Although the initial ER stress response is an adaptive response to restore the ER function, a prolonged ER stress is detrimental to the cell and impairs mitochondrial function (Almanza *et al.,* 2019). The UPR activates a signal transduction pathway through three ER transmembrane proteins: protein kinase-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1α), and activation transcription factor 6 (ATF6). During normal conditions, GRP78 binds and inhibits the activation of these proteins. The mechanism of stress-sensing involves the recognition of unfolded proteins by GRP78, which leads to the dissociation from the sensors and releases the repressive interactive proteins (Ibrahim *et al.,* 2019). Together, PERK, IRE1α and ATF6 coordinate a transcriptional response that decreases protein production and increases protein folding capacity, but if their actions are unable to control a persistent stress they will ultimately lead to apoptosis. The MAMs are involved in the sensing of the ER stress as well as in downstream signaling by PERK, IRE1α, and ATF6. During the initial adaptive phase of the UPR induced by tunicamycin, mitochondria move toward the perinuclear ER, where they form new contacts and tighten the existing ones (Means *et al.,* 2023). During this, ATP is utilized by chaperones, a valosin-containing protein, during ER-associated degradation and the proteasome for degradation of misfolded proteins. Accordingly, an increase in $[ATP]_{ER}$ results from changes in the MAMs dynamics, causing a shift of the cellular metabolic state towards oxidative phosphorylation driven ATP production (Lim *et al.,* 2021). Increased basal mitochondrial Ca^{2+} levels during ER stress might be the result of a combination of an increased $[Ca^{2+}]_{ER}$ leak and MAMs, which exist longer than 105 s, both potentially causing mitochondrial Ca^{2+} overload and apoptosis at a later stage of ER stress (Lim *et al.,* 2021). The activation of the PERK pathway also increases the expression of chaperone proteins related to protein folding, such as Sigma1R (Delprat *et al.,* 2020). The protein Sigma1R can inhibit caspase-4 activation and subsequently plays a protective role under conditions of ER stress (Ni *et al.,* 2021). Sigma1R stabilizes IRE1α at the MAMs upon ER stress, promoting its dimerization and conformational change, and prolonging the activation of the IRE1α/X-box binding protein 1(XBP1) signalling pathway through its endoribonuclease activity and promotes cell survival (Almanza *et al.,* 2019). However, under a prolonged ER stress, Sigma1R translocates from the MAMs to the peripheral ER, potentially decreasing IRE1α signaling and opens the way to apoptosis (Means *et al.,* 2023). Another MAM-localized vesicle-associated membrane protein-associated protein B/C is physiologically involved in activation

of the IRE1α /XBP1 signaling pathway (Vinay Kumar *et al.,* 2014). Except Sigma1R and VAPB, IRE1α RNase activity is regulated at the MAMs by MITOL ubiquitination. PERK is mainly localized at the MAMs and transmits apoptotic signals from the ER to mitochondria. ER stress induces phosphorylation elongation initiation factor 2α (eIF2α) by PERK, which triggers activating transcription factor 4 (ATF4), which in turn activates C/EBP homologous protein (CHOP) leading to apoptosis (Harding *et al.,* 2000). Increasing PERK levels lead to upregulation of some proteins: E3 ubiquitin ligase – Parkin, which prevents mitochondrial fragmentation, and supercomplex assembly factor, which by inhibiting mitochondrial movement enhances mitochondrial respiration and increases contact sites (Balsa *et al.,* 2019). The interaction of PERK with Mfn2 has effects on the UPR and on mitochondrial morphology. Loss of Mfn2 increases mitochondrial fragmentation, but a knockdown of PERK prevents mitochondrial fragmentation caused by Mfn2 loss (Munoz *et al.,* 2013).

Autophagy. Autophagy is a process for the elimination of cellular material to maintain homeostasis through the targeted lysosomal degradation of intracellular material – including damaged organelles and pathogens. Besides, growing evidence has shown that changes in autophagy occur in various human diseases, including tumor, neurological diseases, immune and metabolic disorders (Liu *et al.,* 2022). Numerous studies have shown the key role of MAMs as the location of autophagosome formation (Yang *et al.,* 2020a).

One of the major initiating events in autophagy is the activation of the unc-51-like autophagy-activating kinase (ULK) complex. The ULK1 complex is regulated by upstream kinases, mammalian or mechanistic target of mTORC1 and AMP-activated protein kinase, which sense cellular stresses to deliver the integrated input. Dissociation of mTORC1 from the ULK1 complex during nutrition deprivation and cellular stress results in dephosphorylation of the inhibitory sites and autophosphorylation at the active sites of the complex (Karmacharya *et al.,* 2023). The activated ULK1 complex is then translocated to the MAMs and triggers autophagy initiation.

Mitophagy is a type of autophagy that selectively removes the aged and damaged mitochondria that takes place through two major pathways: dependent on PTEN-induced putative kinase 1 (PINK1) and Parkin (PARK2) or independent of these kinases. Both involve a number of MAM-associated proteins to target mitochondria for degradation (Wang *et al.,* 2011).

Accumulating evidence shows that ER stress plays an important role in inducing mitophagy (Pires *et al.,* 2020). Our previous study (unpublished data) showed an increase in mitophagy in pancreatic cells during ER stress under the conditions of streptozotocin-induced diabetes. It can be assumed that the connection between mitochondria and ER may be another sign of disruption of the interaction mechanisms between organelles under streptozotocin-induced diabetes since the maintenance of a regular MAMs distance was shown to be critical for insulin signaling and affected insulin resistance (Tubbs *et al.,* 2014). By analysing electron microscopy images of pancreatic cells using Fiji software, the MAMs were manually identifed by measuring the distance between the ER and the mitochondria, which typically was between 10 and 20 nm. Contact between the ER and mitochondria was found in two places (***A***); the length of the contacts being 34 and 11 nm, respectively. Also, possible contact is observed in sector (***B***), but the length of the expected contact is outside the normalized limits (**Fig. 1**).

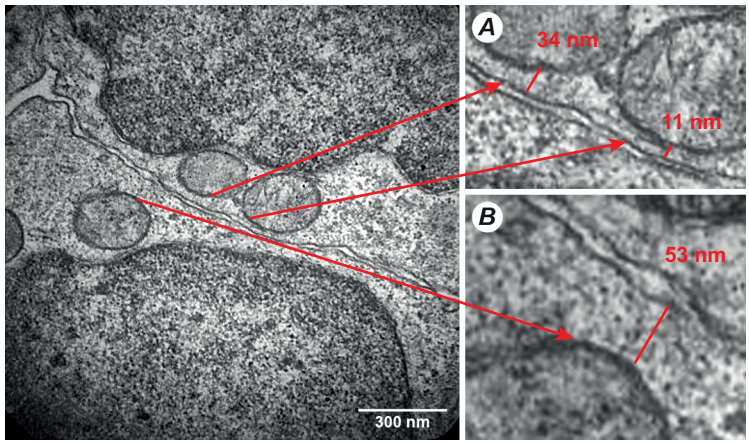

Fig. 1. Electron micrograph of pancreatic tissue of control rats. Showing normal architecture of pancreatic cells: MAMs (arrows) between endoplasmic reticulum (ER) and mitochondria (M)

In **Fig. 2**, we observe the mobilization of mitochondria to the cell periphery in animals with induced diabetes and the formation of MAMs with very tight junctions from 8 nm to 17 nm, compared with the control (11–34 nm). The distance between mitochondria and ER is important for maintaining MAMs homeostasis; a significant reduction in this distance has been observed in central nervous system degeneration, including Alzheimer's disease and Parkinson's disease (Perez-Leanos *et al.,* 2021). Taking into account the above considerations, it is clear that the study of the ER–mitochondria interaction needs a deeper understanding of the molecular events underlying cellular mechanisms in both physiological and pathological conditions.

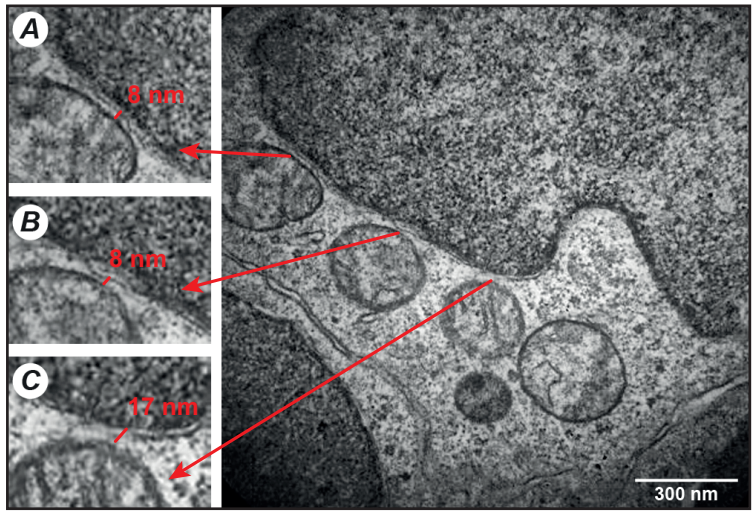

Fig. 2. Electron micrograph of pancreatic tissue of rats with streptozotocin-induced diabetes. Showing normal architecture of pancreatic cells: MAMs (arrows) between endoplasmic reticulum (ER) and mitochondria (M)

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, [O.K.; S.B.;]; methodology, [O.K.; Y.B.]; validation, [O.K.; Y.B.]; formal analysis, [Y.B.].; investigation, [O.K.; Y.B.]; resources, [O.K.; Y.B.]; writing – original draft preparation, [O.K.]; writing – review and editing, [N.S.]; visualization, [Y.B., O.K.]; supervision, [N.S.]; project administration, [N.S.]; funding acquisition, [-].

All authors have read and agreed to the published version of the manuscript.

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СТРУКТУРА ТА ФУНКЦІЇ МЕМБРАН ЕНДОПЛАЗМАТИЧНОГО РЕТИКУЛУМУ, АСОЦІЙОВАНИХ ІЗ МІТОХОНДРІЯМИ, ТА ЇХНЯ РОЛЬ У ДИСФУНКЦІЇ β-КЛІТИН ПІДШЛУНКОВОЇ ЗАЛОЗИ

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Рухливість ендоплазматичних мембран і місць їхнього контакту з органелами є важливим чинником у регуляції клітинного метаболізму та процесів, пов'язаних із життєвим циклом клітини. Мембрани ендоплазматичного ретикулуму, асоційовані з мітохондріями (mitochondria-associated membranes, MAMs), є ключовими сигнальними центрами забезпечення ліпідного й кальцієвого гомеостазу, транспортування активних форм Оксигену, регуляції аутофагії та мітохондріальної динаміки. В останні роки MAMs посідають центральне місце у багатьох дослідженнях, пов'язаних із ідентифікацією білків MAMs і визначенням їхньої ролі у передачі різноманітних сигналів. Завдяки багатьом дослідженням було доведено важливість MAMs для підтримки нормального функціонування як мітохондрій, так і ЕР. Відомо, що надмірне утворення MAMs зумовлює каскад патологічних подій, таких як надмірне надходження кальцію в мітохондрії, аномальні рівні ліпідів, утворення аутофагосом і, зрештою, апоптоз клітин. У цій статті ми в основному зосереджуємо увагу на будові та функції MAMs, більш конкретно розглянувши роль MAMs у регуляції транспортування Ca^{2+}, розвитку стресу ЕР, участі у злитті й поділі мітохондрій, а також аутофагії. Змінену взаємодію між ЕР та мітохондріями спостерігають за різноманітних функціональних змін у клітинах підшлункової залози, тим самим розкриваючи роль MAMs у гомеостазі глюкози та розвитку цукрового діабету. Розвиток мітохондріальної дисфункції, стресу ЕР і оксидативного стресу є причиною дисфункції β-клітин підшлункової залози. Ймовірно, MAMs, регулюючи передачу сигналів між ЕР і мітохондріями, відіграють важливу роль у перебігу цих процесів у клітинах підшлункової залози за патологій. Було з'ясовано, що за стрептозотоцин-індукованого діабету в клітинах підшлункової залози підвищений рівень мітофагії пов'язаний зі зменшенням міжмембранної відстані у MAMs. З урахуванням наведених вище міркувань, стає зрозуміло, що вивчення взаємодії різних структурних компонентів MAMs як у нормі, так і за патологічних станів може забезпечити розробку важливих терапевтичних стратегій.

Ключові слова: мітохондрії, ендоплазматичний ретикулум, MAMs, стрес ЕР, мітофагія

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