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Review

Endoplasmic reticulum-mitochondria Ca^{2+} crosstalk in the control of the tumor cell fate

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ABSTRACT

Mitochondria-associated membranes are juxtaposed between the endoplasmic reticulum and mitochondria and have been identified as a critical hub in the regulation of apoptosis and tumor growth. One key function of mitochondria-associated membranes is to provide asylum to a number of proteins with tumor suppressor and oncogenic properties. In this review, we discuss how Ca^{2+} flux manipulation represents the primary mechanism underlying the action of several oncogenes and tumor-suppressor genes and how these networks might be manipulated to provide novel therapies for cancer. This article is part of a Special Issue entitled: ECS Meeting edited by Claus Heizmann, Joachim Krebs and Jacques Haiech.

1. Introduction

Mitochondria and endoplasmic reticulum (ER) membranes are the most abundant in the average animal cell and about 5–20% of the mitochondrial membranes are directly in contact with the ER. About 50% of the total cell membrane is occupied by ER, followed by Golgi apparatus and mitochondria (about 30%). These membranes have been discovered and characterized only in 1990, when they were described as tight contacts between the ER and mitochondria structurally and functionally modulated through a series of molecular bridges formed at specific subdomains of the ER membrane, defined mitochondria-associated membranes (MAMs) [1].

ER is responsible for the synthesis of lipids and assists in the transport to the extracellular space or to the cell membrane and the modification of various proteins. It is also considered a signaling organelle, since it regulates a wide range of intracellular processes including Ca^{2+} homeostasis, unfolded protein response (UPR), autophagy, redox regulation and apoptosis [2]. Mitochondria primarily supply the necessary energy to the cell. Beyond this feature, they serve as a signaling platform where the physiology of the cells is influenced and acts as transducer and effector in multiple processes including Ca^{2+} signaling, growth factor signaling, differentiation, apoptosis, hypoxic stress responses and innate immunity [3–5]. MAMs have been widely described as a pivotal hub regulating the most important cellular pathways controlling cell fate [6]. An increasing number of studies suggest that ER and mitochondria play a key role in several human diseases further expanding the important role of these two organelles hold in the life of the cell [7]. Therefore, it is not surprising that MAMs are also involved in several cellular processes as well as in the progression of numerous pathologies [8]. First evidence of a link between MAMs and inflammation dates back to 2011 when Zhou and coworkers established that upon inflammasome activation both NLR family pyrin domain containing 3 (NLRP3) and its adaptor apoptosis-associated speck-like protein containing CARD (ASC) co-localize with ER and mitochondria organelle clusters [9]. In addition, dysfunction of the MAMs has also been related to neurodegenerative diseases, such as Parkinson's and Huntington's

Abbreviations: AIF, apoptosis-inducing factor; ASC, adaptor apoptosis-associated speck-like protein containing CARD; BRCA1, breast/ovarian cancer susceptibility gene 1; ER, endoplasmic reticulum; ERp44, ER resident protein 44; FACL4, long-chain fatty acid-CoA ligase type 4; GRP75, glucose-regulated protein; GRP78, 78 kDa glucose-regulated protein; HK2, phosphorylates hexokinase 2; IMM, inner mitochondrial membrane; IP3R, inositol 1,4,5-triphosphate receptor; MAMs, mitochondria-associated membranes; Mcl-1, myeloid cell leukemia factor 1; MCU, mitochondrial Ca^{2+} uniporter; MFN, mitofusin; mPTP, mitochondrial permeability transition pore; mTORc2, mammalian target of rapamycin complex 2; NLRP3, NLR family pyrin domain containing 3; OMM, outer mitochondrial membrane; PACS-2, phosphofurin acid cluster sorting protein 2; PML, promyelocitic leukemia protein; PP2a, protein phosphatase 2a; PSS-1, phosphatidylserine synthase-1; PtdSer, phosphatidylserine; PtdCho, phosphatidylcholine; ROS, reactive oxygen species; SERCA, Sarco/Endoplasmic Reticulum Calcium ATPase; Sig1-R, sigma-1 receptor; TMX1, thioredoxin-related transmembrane protein; TXNIP, thioredoxin-interacting protein; UPR, unfolded protein response; VDACs, voltage-dependent anion channels.

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[10]. Furthermore, several studies support the role of the MAMs compartment as a central core involved in skeletal and cardiac muscle physiopathology [11]. Lastly, MAMs have been extensively studied in cancer research. As a matter of fact, since Jean Vance discovered these membranes in 1990, a plethora of oncogenes and tumor suppressor genes have been found in these molecular bridges [8,12,13]. For instance, sigma-1 receptor (Sig1-R) and 78 kDa glucose-regulated protein (GRP78) maintain correct MAMs integrity, which is crucial for cell survival [14]. Sig1R is also established as an interorganelle signaling modulator involved in MAM's regulation of cell survival by enhancing IRE1 stability which in turn leads to travelling of the reactive oxygen species (ROS) message from mitochondria to the nucleus and attenuation of ER stress [15]. Other proteins such as ERO1-alpha and protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) prevent oxidative stress and support correct protein folding that are strong ER-stress inducers and mediators of cell death programs, such as apoptosis and necrosis [16]. The key primary function of MAMs-resident proteins (e.g., AKT, promyelocitic leukemia protein (PML), RAS and protein phosphatase and tensin homolog deleted on chromosome 10(PTEN)) is to control Ca^{2+} homeostasis. Notably, several cancers display corrupted activity of these proteins and, consequently, alterations in Ca^{2+} signaling events that are a crucial factor in controlling cell death and survival [17] (Fig. 1).

2. MAMs structure

The mitochondria and the ER are dynamic organelles that undergo continuous membrane remodeling, fusion and fission, as well as redistribution in the intracellular space. Two approaches have been developed to test the hypothesis that interactions between mitochondria and ER occur: the first consists in the study of the direct exchange of Ca^{2+} ions between the ER and mitochondria; the second consists in microscopic visualization or isolation of interacting regions.

Detailed morphological [18] and electron tomography studies [19] revealed the presence of overlapping regions between ER and mitochondria and the distance between these two organelles was approximately 10 to 25 nm at the contact sites, suggesting an interaction between the opposing membrane faces of both ER and mitochondrial side and a physical association of ER proteins with components of the outer mitochondrial membrane (OMM). Importantly, although the ER and mitochondrial membranes form specific contact sites, they do not fuse, thereby maintaining the organelle distinct structures [20]. Rizzuto and coworkers evaluations showed that approximately 20% of the mitochondrial surface could be in direct contact with the ER [18], strengthening the idea of the existence of physical links between them. Indeed, the random and dynamic apposition between ER membrane and mitochondria is dependent on intracellular signaling and this suggests that their interaction is also a transient phenomenon. Nowadays, the development of novel experimental procedures has enabled scientists to isolate pure MAM fractions from yeast, different organs and tissues, as well as various cell lines [21]. The optimized protocol is based on work By J.E Vance who first described the isolation and the characterization of a “fraction X” that is associated to mitochondria and has many similarities to microsomes [1].

An isolate MAM fraction is composed of membrane fragments both from the OMM and the ER that had been closely related at the time of fractionation. The ER portion of the MAM fraction has been recently regarded as a detergent resistant lipid raft [22].

Mitochondria require a continuous and coordinated supply of membrane lipids to carry out their physiological processes and maintain their membrane integrity [23]. Initially, the MAM fraction was described as a center of lipid synthesis and non-vesicular trafficking between the ER and mitochondrial membranes based on the presence of long-chain fatty acid-CoA ligase type 4 (FACL4) and phosphatidylserine synthase-1 (PSS-1) enzymes and, for this reason, it is involved in cycles of synthesis of phosphatidylserine (PtdSer) and phosphatidylcholine (PtdCho). These are phospholipid- and glycosphingolipid-synthesizing enzymes required for cholesterol and ceramide biosynthesis, enzymes involved in glucose metabolism and supporting direct transfer of lipids between the ER and mitochondria [24]. Recently, Aufschnaiter et al. reported that the modification of lipid composition in mitochondria and MAMs decisively impacts neurodegeneration-associated cell death [25]. The ER and mitochondrial networks not only control different aspects of cellular metabolism but, through their close and dynamic interaction, are also involved in transmission of physiological and pathological Ca^{2+} and ROS signals directly from the ER to the mitochondria.

In the last decade, many studies have focused on revealing the molecular components of the MAM fraction. ER-mitochondria connection contains several crucial proteins involved in many biological pathways [12]. In the last years, different proteomic studies of MAMs isolated from human skin [26] and mouse brain cells [27] have identified approximately 1000 MAM proteins. The mutual affinities between MAM proteins reinforce the interaction between intracellular components, improving the half-life of their interaction. More recently, Sala-Vila performed in-depth mass spectrometry analysis of the proteins comprising MAM-enriched fractions identifying 1052 proteins among which

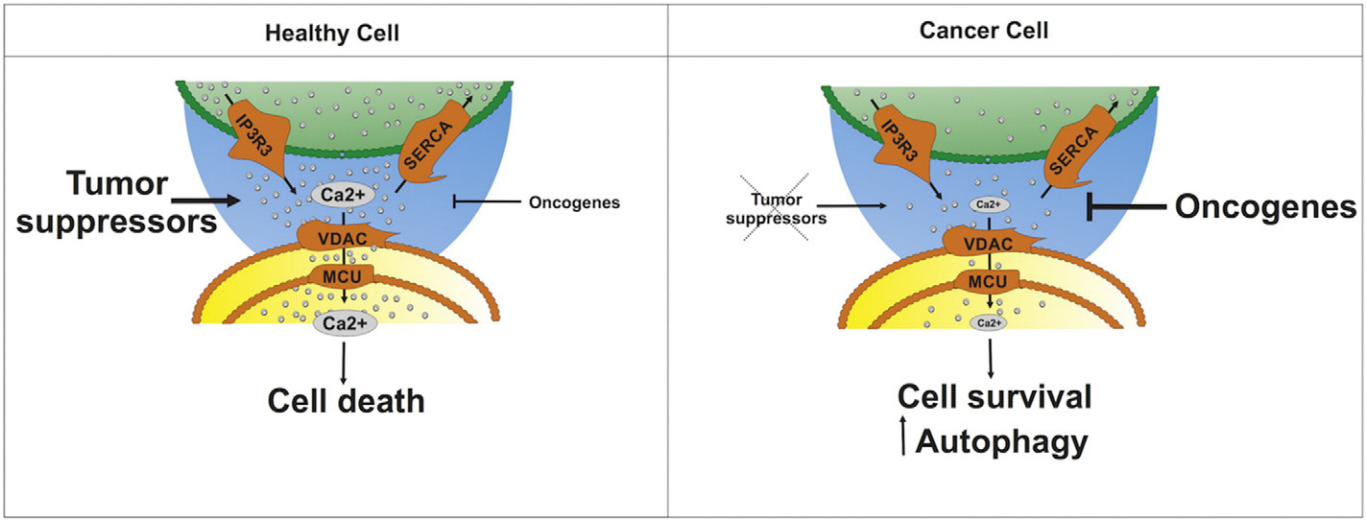

Fig. 1. ER-mitochondrial Ca^{2+} signaling mediated by tumor suppressor and oncogenes in healthy cells and in cancer cells. Tumor suppressors stimulate ER-mitochondrial Ca^{2+} fluxes favoring cell death (left panel), whereas oncogenes promote cell survival by suppressing pro-apoptotic ER-mitochondrial Ca^{2+} signaling events (right panel).

caveolin-1 (CAV1) as an integral component of hepatic MAMs, which determine the relative cholesterol content of these ER subdomains [28]. Indeed, MAMs participate and have a pivotal role in numerous cellular processes, including calcium handling [29] [as indicated by the presence of inositol 1,4,5-triphosphate receptor (IP3R), ryanodine receptor and Sarco/Endoplasmic Reticulum Calcium ATPase (Serca)], inflammation [some proteins essential for NLRP3 inflammasome formation and thioredoxin-interacting protein (TXNIP) binding to NLRP3], protein sorting [e.g. phosphofurin acid cluster sorting protein 2 (PACS-2)], ER stress [e.g., ER resident protein 44 (ERp44) and 75 kDa glucose-regulated protein (GRP75) have been localized at ER-mitochondria contact sites], lipid synthesis, trafficking, and apoptosis (e.g., p53, Sig1R, PML and Bcl-2 have been localized at these sites) (Table 1) [8].

A key role for ER-mitochondria interactions is also played by mitochondria-modelling and chaperone proteins. Mitofusin (MFN)-1 and MFN-2 stabilize the interaction between adjacent mitochondria, regulate ER morphology and Ca^{2+} homeostasis, and directly tether ER to mitochondria, thus facilitating efficient Ca^{2+} uptake by mitochondria [30]. However, this established Mfn2 function has been recently questioned, calling for a critical re-evaluation of the role of Mfn2 in ER–mitochondria crosstalk. Using a multiplicity of morphological, biochemical, functional, and genetic approaches, Filadi and colleagues proposed a revised model for ER–mitochondria tethering in which Mfn2 negatively modulates the number of close contacts between the two organelles [31]. Mfn2 ablation increases the structural and functional ER–mitochondria coupling and increases ER and mitochondria membrane association leading to higher sensitivity to mitochondrial Ca^{2+}-dependent cell death.

Recently, Naon D. et al. decided to critically re-evaluate if chronic or acute Mfn2 ablation impacts on ER–mitochondria proximity and Ca^{2+} transfer [32], discrediting the proposed role for Mfn2 as a negative regulator of tethering [31]. Functionally, this process reduces mitochondrial Ca^{2+} uptake without altering the mitochondrial Ca^{2+} uniporter complex in multiple tissues. Thus, the discoveries of the role of ER–mitochondria juxtaposition in cell biology based on Mfn2 as a tool remain unchallenged.

However, the localization of some proteins in the MAMs fraction and the extent of their enrichment are still under debate because their connection to the MAM fraction is unclear.

MAMs have pivotal roles in several cellular functions, primarily a highly efficient transmission of Ca^{2+} from the ER to the mitochondrial network that stimulates oxidative metabolism and, contrariwise, might enable the metabolically energized mitochondria to regulate ER Ca^{2+} homeostasis. Indeed, Ca^{2+} ions, released from the ER by IP3Rs, cross the freely permeable OMM through voltage-dependent anion channels (VDACs) [33], reach the inner mitochondrial membrane (IMM), and accumulate in the matrix via the mitochondrial Ca^{2+} uniporter (MCU) complex, thanks to this microdomains which overcome the low apparent Ca^{2+} affinity of the MCU [34,35]. However, the excessive Ca^{2+} influx and accumulation in mitochondrial matrix induces release of pro-apoptotic factors, as cytochrome *c*, SMAC/DIABLO and apoptosis-inducing factor (AIF), into the cytosol and consequently apoptosis, triggered by opening of the mitochondrial permeability transition pore (mPTP) [36].

Furthermore, the ER and mitochondria are two of the major sites for ROS production inside the cell and many regulators of the oxidative state of the cell are localized at the MAMs (for a detailed review see [8,37]). Recently, Booth and colleagues, employing drug-inducible synthetic ER-mitochondrial linkers, have demonstrated that the ER-mitochondrial interface hosts a nanodomain of H_2O_2 (originated from the mitochondrial cristae) which represents a component of inter-organelle communication, regulating calcium signaling and mitochondrial activities [38].

As far as MAMs are concerned, an interesting example of a MAMs-resident ROS-generating protein is p66Shc [39]. Under oxidative stress p66Shc can participate in the signaling pathway leading to apoptosis. Also beyond p66Shc, ER chaperones and oxidoreductases are important regulators of tumor growth. Under conditions that lead to low oxygen supply and ER stress, ER oxidoreductases and chaperones not only can promote the folding of proteins, but also alter the properties of the plasma membrane and hence modulate tumor immune recognition (for an extensive review see [40]). Understanding the roles and mechanisms of ER chaperones in regulating tumor cell functions and immunorecognition will lead to important insights for the development of novel anti-cancer therapies.

MAMs could now be considered as a domain of the ER enriched with numerous ER chaperones [41]. The Ca^{2+}-binding and quality control chaperon calnexin, in addition to thioredoxin-related transmembrane protein (TMX1), resides at MAMs [42] and its localization is mediated by palmitoylation of membrane-proximal, cytosolically exposed cysteine residues and, only partially, by the interaction with the ER sorting molecule PACS2 [43].

Recently, the redox-sensitive oxidoreductase TMX1 has been demonstrated to inhibit the calcium pump SERCA2b at ER-mitochondria contact sites, thereby affecting ER-mitochondrial calcium transfer and mitochondrial bioenergetics [29,44]. Cancer cells with low TMX1, exhibit increased ER Ca^{2+} flux, accelerated cytosolic Ca^{2+} clearance, and reduced Ca^{2+} transfer to mitochondria. Thus, low levels of TMX1 reduce ER–mitochondria contacts, shift bioenergetics away from mitochondria, and accelerate tumor growth [44].

Taken together, these findings highlight the involvement of MAMs-mediated disturbances in the pathogenesis of a variety of diseases involving MAMs.

3. Cancer-related Ca^{2+} dysfunctions at MAMs

As previously mentioned, MAMs are not simply a static bridge between the ER and mitochondria, but dynamic organelles that play a variety of roles being crucial for numerous physiological processes. In

Table 1
Summary of the most important proteins involved in the regulation of ER-mitochondrial Ca^{2+} fluxes and their impact on tumor cell fate processes, as discussed in this review.

Protein	Impact on ER-mitochondrial Ca^{2+} transfer	Impact on tumor cell fate	References
TMX1	Affects ER-mitochondrial calcium transfer inhibiting Serca2b	Proapoptotic	[29,41]
AKT	Inhibition of Ca^{2+} release from ER	Antiapoptotic	[43–47]
VDAC1	Interacts with IP3Rs and provides molecular route for the higher sensitivity of the Ca^{2+} transfers	Proapoptotic	[49]
Bcl-2	Induction of Ca^{2+} leakage from ER	Antiapoptotic	[52,53]
Bcl-XL	Induction of Ca^{2+} leakage from ER	Antiapoptotic	[54–56]
H-Ras12v	Reduction of ER Ca^{2+} levels and suppression of Ca^{2+} influx to mitochondria	Antiapoptotic	[62]
Sig-1R	Regulation of Ca^{2+} homeostasis between the ER and the mitochondria	Antiapoptotic	[14]
mTORc2 (mTOR complex 2)	Regulation of Ca^{2+} uptake	Antiapoptotic	[47]
FATE1	Modulation of ER-mitochondria distance	Antiapoptotic	[66]
PTEN	Regulation of Ca^{2+} release via IP3R3	Proapoptotic	[67]
PML	Modulation of the ER-mitochondria Ca^{2+} flux	Proapoptotic	[68,69]
p53	Modulation of Ca^{2+} transfer from ER to mitochondria interacting with Serca	Proapoptotic	[74]
Mcl-1	Induction of Ca^{2+} leakage from ER	Antiapoptotic	[58]

particular, MAMs are enriched in many oncosuppressors and oncogenes that are localized at ER-mitochondria membranes where they can alter MAM functions and modulate different cell death programs [45] (Fig. 2). In recent years, it has been shown that the function and behavior of MAMs are central to the main molecular pathways of human cells and, consequently, MAM dysfunction has been associated with several types of cancer.

Among oncogenes, the serine/threonine kinase AKT has been physically and functionally linked to MAMs; in fact, several studies have demonstrated that AKT mediates the phosphorylation of IP3R type 3, inhibiting ER Ca^{2+} fluxes and apoptosis [46–48]. AKT also phosphorylates hexokinase 2 (HK2) promoting its association with the MAM protein VDAC1 and preventing Ca^{2+}-dependent apoptotic response [49]. The AKT activator mammalian target of rapamycin complex 2 (mTORc2) can localize to MAMs where it controls growth factor-mediated MAMs integrity, Ca^{2+} flux, and mitochondrial physiology. mTORC2 controls MAM integrity and mitochondrial function via AKT mediated phosphorylation of the MAMs associated proteins IP3R, HK2 and PACS2 [50].

Noteworthy, VDAC1 is associated with the MAMs and controls metabolic cross-talk between mitochondria and the rest of the cell by allowing the influx and efflux of metabolites, ions, nucleotides, Ca^{2+} and more [51]; so it's not surprising that it has a key function in Ca^{2+} homeostasis, protection against oxidative stress, regulation of apoptosis and involvement in several diseases. VDAC1 (but not isoforms 2 or 3) selectively interacts with IP3Rs [52] and it has a crucial position on the route transferring Ca^{2+} signals from the ER to mitochondria, and thus couples ER and mitochondrial functions. Furthermore, VDAC1 is overexpressed in many cancer types and VDAC1-based peptides, as pro-apoptotic compounds, can be used to potentiate the efficacy of conventional chemotherapeutic agents. In fact, in cancer cells, HK-I and HK-II are overexpressed and promote the detachment of HK from its mitochondrial binding site mediated by VDAC1-based peptides. This could represent a promising anti-cancer strategy [53].

As in the case of AKT, Bcl-2, the first oncogene to be linked to a Ca^{2+}-dependent cancer activity, is highly enriched at MAMs [54] acting at both the ER and the mitochondrial sides to exert its anti-apoptotic function. At the ER side, Bcl-2 promotes survival by limiting Ca^{2+} release from the ER to the mitochondria, interacting directly with IP3R to inhibit channel opening and ER Ca^{2+}-release [55], thus inhibiting apoptosis. At the mitochondrial side, Bcl-2 binds Bax/Bak via its hydrophobic groove composed of BH1, 2 and 3, preventing their oligomerization and inhibiting Bax/Bak formation [56].

Other members of the Bcl-2 protein family, Bcl-xL and the myeloid cell leukemia factor 1 (Mcl-1), two anti-apoptotic proteins, have been described at MAMs. Bcl-xL, a proto-oncogene expressed in many tissues and frequently overexpressed in several cancers, can directly interact with IP3Rs, increase its sensitivity to inositol 1,4,5-trisphosphate and reduce ER Ca^{2+} release. As a consequence, cells are protected against apoptosis through a Ca^{2+}-dependent mechanism between ER and mitochondria, enhancing cellular bioenergetics and enhancing survival [57]. Interestingly, Bcl-xL interacts with VDAC1 and VDAC3 but not VDAC2 promoting matrix Ca^{2+} accumulation by increasing Ca^{2+} transfer across the outer mitochondrial membrane [58]. At the MAMs, Bcl-xL can regulate apoptosis by i) modulating Ca^{2+} uptake into the mitochondria and rendering cells more resistant to increased Ca^{2+} release from the ER, ii) targeting VDAC1 and inhibiting apoptosis by decreasing VDAC1-mediated Ca^{2+} uptake into the mitochondria [59]. At the

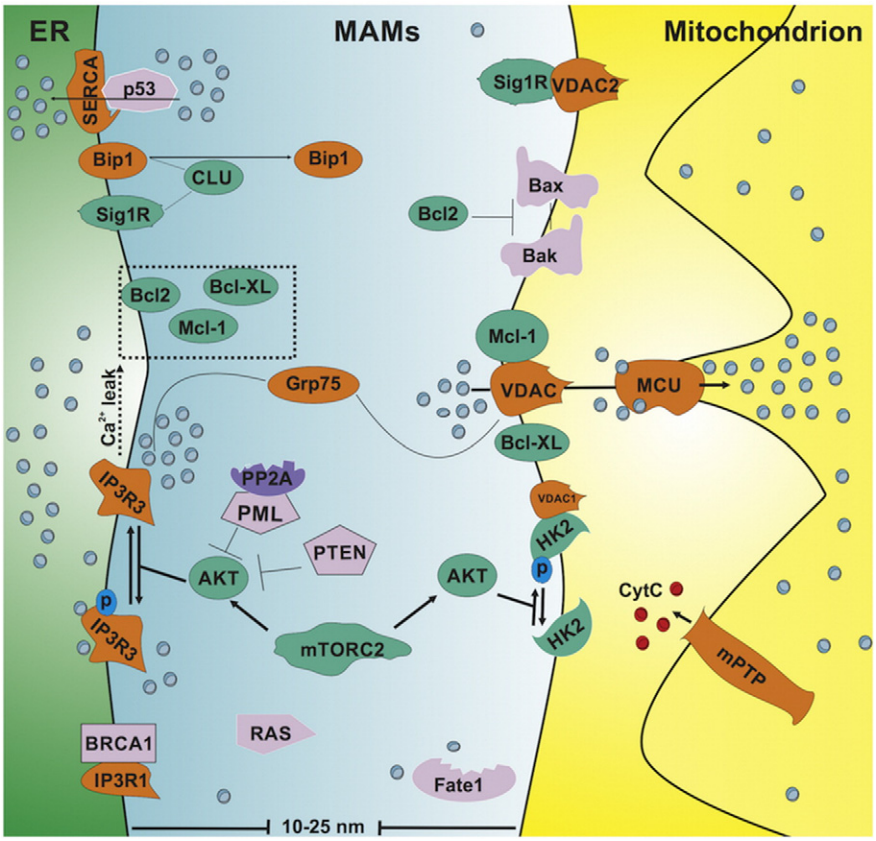

Fig. 2. Oncosuppressors and oncogenes at mitochondria-associated membranes modulate different cell death programs. Oncogenes are indicated in green, and tumor suppressors are depicted in purple. Key players involved in Ca^{2+} signaling are shown in orange. Bak, Bcl-2 antagonist/killer; Bax, Bcl-2 associated X protein; Bcl-2, B-cell CLL/lymphoma 2; BIP1, or GRP78, glucose regulated protein 78; CLU, clusterin; cyt. *c*, cytochrome *c*; ER, endoplasmic reticulum; GRP75, glucose regulated protein 75; HK2, hexokinase 2; IP3R, inositol 1,4,5 trisphosphate receptor; MAMs, mitochondria associated membranes; Mcl-1, myeloid cell leukemia sequence 1; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; mTORC2, mechanistic target of rapamycin complex 2; PML, promyelocytic leukemia protein; PTEN, phosphatase and tensin homolog deleted on chromosome 10; SERCA, sarco/endoplasmatic reticulum Ca^{2+} ATPase; Sig1-R, Sigma 1 receptor; VDAC, voltage-dependent anion channel.

mitochondria, Bcl-xL can regulate apoptosis independently and more effectively than Bcl-xL at the ER, facilitating ER-to-mitochondrial Ca^{2+} transfer, enhancing mitochondrial bioenergetics and subsequently rendering cells better able to withstand apoptotic challenges [60].

Mcl-1, another member of the Bcl-2-family, has been implicated in the binding of IP3Rs, providing apoptosis resistance that impinges on cellular Ca^{2+} homeostasis [61]. Interestingly, one study reported that Mcl-1 promotes lung cancer cell migration by directly interacting with VDAC thereby increasing mitochondrial Ca^{2+} uptake and ROS generation [62]. In addition, our group demonstrated that Mcl-1 controls mitochondrial dynamics by promoting Drp1-mediated mitochondrial fission, preventing mitochondrial hyperpolarization and Ca^{2+} uptake [63]. A direct link between Ca^{2+} regulation and mitochondrial biology in cancer has been described for the oncogene H-RAS (H-Ras12v) which has also been localized to the MAM compartment [64]. In this work, Rimessi and coworkers showed that Ca^{2+} signaling has an important role in tumor formation and maintenance promoted by compartmentalized H-Ras. Moreover, oncogenic K-RAS inhibits Ca^{2+} release from ER reducing ER Ca^{2+} levels and suppressing Ca^{2+} influx to mitochondria, as observed in colon cancer cell lines [65]. One of the best–characterized calcium regulatory proteins is Sig1-R. Sig1-R, which has been implicated in carcinogenesis, is a Ca^{2+}-sensitive and ligand-operated receptor chaperone and localizes at MAMs, stabilizes the conformation of IP3R type 3 and the ER stress sensor IRE1. Normally, Sig1-R forms a complex at MAMs with the chaperone BiP/GRP78 to regulate Ca^{2+} homeostasis between the ER and the mitochondria, but upon Ca^{2+} depletion or via ligand stimulation, Sig1-R dissociates from BiP, leading to a prolonged Ca^{2+} signaling into mitochondria via IP3R3 [14]. These findings support the findings reported by Wu Z. and Bowen A.D. who suggested that the sigma-1 receptor binds to ankyrin B 220 via its C-terminal region and causes dissociation from the IP3 receptor. This results in sensitization of the cells to bradykinin-stimulated Ca^{2+} release by increasing the amount of ankyrin-free IP3R3 [66].

Moreover, a recent report has shown that Sig1R is physically associated with VDAC2, a mitochondrial channel involved in cholesterol import into the mitochondria for metabolic regulation [67]. Recently, Sig1R has been demonstrated to mediate the cross-talk between cancer cells and their microenvironment, thus driving oncogenesis by shaping cellular electrical activity in response to extracellular signals [68]. In fact, Sig1R dynamically controls the membrane expression of the human voltage-dependent K+ channel human ether-à-go-go-related gene (hERG) in myeloid leukemia and colorectal cancer cell lines, promoting the formation of hERG/β1-integrin signaling complexes upon extracellular matrix stimulation, triggering the activation of the phosphoinositide 3 kinase/AKT pathway [68].

While no data is available on the function of MAM-associated Sig1R in tumors, it is conceivable that Sig1R contributes to the adaptation of cancer cells in a restrictive environment.

A recent study has demonstrated that fetal and adult testis expressed (FATE1), a protein overexpressed in a variety of cancers, is localized at MAMs and is implicated in the regulation of Ca^{2+}- and drug-dependent apoptosis in cancer cells by modulating ER–mitochondria distance [69].

In addition, to its interaction with cancer-related proteins, MAMs are having an emerging role in controlling cell death due to the fact that numerous tumor suppressors are localized in this intracellular localization. The tumor suppressor PTEN is among the most commonly lost or mutated tumor suppressors implicated in human cancers, and it is a key regulator of a wide range of biological functions other than tumor suppression. Recent findings have shown that it localizes at MAMs where it interacts with the IP3R3 and regulates Ca^{2+} release from the ER in a protein phosphatase-dependent manner that counteracts AKT activation; thus, it can inhibit AKT-mediated phosphorylation of IP3R3, which protects from Ca^{2+}-mediated apoptosis [70]. The tumor suppressor PML also modulates the ER-mitochondria Ca^{2+} flux and apoptosis. At the nucleus, PML performs its pro-apoptotic function forming multiprotein nuclear macromolecular structures called PML-nuclear bodies. Our laboratory has demonstrated that PML also localizes at the ER/MAMs where it modulates IP3R3 activity and the ER–mitochondria Ca^{2+} fluxes by promoting the formation of a multiprotein complex containing IP3R3, AKT and the protein phosphatase 2A (PP2a) [71]. Indeed, loss of PML promotes a reduced PP2a activity at the ER and an increase in AKT activity, leading to IP3R3 hyperphosphorylation. As described above, this inhibits ER Ca^{2+} release and transfer to mitochondria leading to inhibition of apoptosis.

A recent study by our group has demonstrated that PML localized at MAMs is fundamental not only for apoptosis control but also because it plays a key role in the control of autophagy in a Ca^{2+}-dependent manner, through the AMPK/mTOR/Ulk1 pathway [72]. To verify whether down-regulated ER-mitochondrial Ca^{2+} transfer is õimportant for the induction of autophagy we overexpressed MCU in PML KO cells and we demonstrated that increasing the ability of mitochondria to accumulate Ca^{2+} was sufficient to repress autophagy by reducing the amount of activated AMPK, suggesting that PML controls autophagy at MAMs by exerting its effects on Ca^{2+} homeostasis [72]. The loss of PML from MAMs confers contemporary õresistance to apoptotic stimuli and metabolic stress, promoting cell survival in the tumor environment.

Recently, Cardenas' and Foskett' teams have elucidated a novel and critical role for basal ER–mitochondrial Ca^{2+} fluxes and their Ca^{2+}-transport systems in tumor cell survival [73,74]. These studies demonstrate that different tumorigenic cancer cell lines require constitutive ER-to-mitochondria Ca^{2+} transfer for their survival; in fact, inhibition of InsP3R with Xestospongin B reduces the proliferative potential of cancer cell lines that die by necrosis but not by autophagy, apoptosis or necroptosis [74]. However, due to the complexity of the role of IP3Rs and ER–mitochondrial Ca^{2+} flux in tumor survival, additional work is needed to completely understand the strong and selective dependence of tumors on IP3Rs and Ca^{2+} signaling and the pathways involved in their survival [75].

Other oncosuppressors show anti-cancer activities linked to the rearrangement of Ca^{2+} dynamics. These include the tumor suppressor breast/ovarian cancer susceptibility gene 1 (BRCA1) that physically and functionally interacts with IP3R-1 and increases its activity [76]. Therefore, BRCA1 mediates its pro-apoptotic effects by binding to and modulating apoptotic calcium release through the IP3R.

The tumor suppressor p53 regulates tumorigenesis in a Ca^{2+} dependent pathway. Different reports have documented the ability of p53 to regulate cell fate via post-translational modifications; however, p53 was recently shown to localize to the ER and MAMs, where it functions in modulating Ca^{2+} transfer from ER to mitochondria [77]. p53 physically interacts with SERCA and this increases the efficiency of the transfer of Ca^{2+} ions between the ER and mitochondria, augmenting the propensity of (pre)malignant cells exposed to oncogenic or chemotherapeutic stress to succumb to apoptosis. The interplay between p53 and Ca^{2+} signaling is not limited to chemotherapy but is also relevant for cellular response following photodynamic therapy (PDT) [78]. Giorgi and colleagues demonstrated that extra-nuclear p53 promotes pro-apoptotic Ca^{2+} signaling at the ER-mitochondria and, consequently, triggers apoptotic cell death after PDT treatment.

These concepts were validated both in vitro and in vivo by investigating Ca^{2+} signaling and cell death in three-dimensional tumor masses [78], suggesting that functional p53 is needed to generate an efficient Ca^{2+} response after PDT treatment that induce apoptosis, limiting tumor growth. The vast implications of Ca^{2+} signaling on various intracellular signaling mechanisms demonstrate the importance of the MAMs for metabolism and cellular lifespan. Considering that several tumor suppressor genes and proteins with oncogenic properties linked to MAMs are deeply involved in cancer progression, there is growing interest in novel therapeutic approaches based on MAM manipulation.

4. Concluding remarks

From the biochemical identification of MAMs in 1990, we have witnessed a large increase in the body of knowledge of MAM structure, as well as MAMs-related physiological functions. As a consequence, MAM dysfunctions have been linked to different pathological conditions including cancer, obesity and neurological disorders, such as Alzheimer's and Parkinson's disease. Importantly, a drastic dysregulation in Ca^{2+} signaling has also been associated to these pathological states implying that Ca^{2+} communication between ER and mitochondria is vital for the physiological functioning of several intracellular processes. In addition, the MAMs host several oncogenes and tumor suppressors that exert their functions though Ca^{2+} modulation and these membranes play a key role in the transmission of ROS-mediated signals. Therefore, the comprehension of MAM molecular composition and dynamics, as well as the identification of novel pharmacological approaches, aimed to re-establish MAM integrity and the physiological Ca^{2+} transfer between the two organelles, could establish the MAM compartment and its proteins as a key target for the development of novel therapeutic approaches.

Transparency document

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

Conflict of interest

The authors declare no conflict of interest.

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