Biochimica et Biophysica Acta 1833 (2013) 213–224

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Where the endoplasmic reticulum and the mitochondrion tie the knot: The mitochondria-associated membrane (MAM)☆

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ARTICLE INFO

Article history:
Received 26 January 2012
Received in revised form 12 April 2012
Accepted 25 April 2012
Available online 2 May 2012

Keywords:
Endoplasmic reticulum (ER)
Mitochondria
Mitochondria-associated membrane (MAM)
Lipid metabolism
Calcium signaling

ABSTRACT

More than a billion years ago, bacterial precursors of mitochondria became endosymbionts in what we call eukaryotic cells today. The true significance of the word "endosymbiont" has only become clear to cell biologists with the discovery that the endoplasmic reticulum (ER) superorganelle dedicates a special domain for the metabolic interaction with mitochondria. This domain, identified in all eukaryotic cell systems from yeast to man and called the mitochondria-associated membrane (MAM), has a distinct proteome, specific tethers on the cytosolic face and regulatory proteins in the ER lumen of the ER. The MAM has distinct biochemical properties and appears as ER tubules closely apposed to mitochondria on electron micrographs. The functions of the MAM range from lipid metabolism and calcium signaling to inflammasome formation. Consistent with these functions, the MAM is enriched in lipid metabolism enzymes and calcium handling proteins. During cellular stress situations, like an altered cellular redox state, the MAM alters its set of regulatory proteins and thus alters MAM functions. Notably, this set prominently comprises ER chaperones and oxidoreductases that connect protein synthesis and folding inside the ER to mitochondrial metabolism. Moreover, ER membranes associated with mitochondria also accommodate parts of the machinery that determines mitochondrial membrane dynamics and connect mitochondria to the cytoskeleton. Together, these exciting findings demonstrate that the physiological interactions between the ER and mitochondria are so bilateral that we are tempted to compare their relationship to the one of a married couple: distinct, but inseparable and certainly dependent on each other. In this paradigm, the MAM stands for the intracellular location where the two organelles tie the knot. Resembling "real life", the happy marriage between the two organelles prevents the onset of diseases that are characterized by disrupted metabolism and decreased lifespan, including neurodegeneration and cancer. This article is part of a Special Issue entitled: Mitochondrial dynamics and physiology.

1. Introduction

More than 20 years ago, Jean Vance biochemically isolated an intracellular structure from rat liver that she defined as physical contacts between the endoplasmic reticulum (ER) and mitochondria and termed this membrane fraction the mitochondria-associated membrane (MAM) [1]. At that point, the ER had been recognized for many years as the point where the secretion of newly synthesized proteins destined to the Golgi complex and the plasma membrane originates [2,3]. Over the years however, numerous researchers noted the extraordinary difficulty to biochemically separate ER and mitochondria [4,5], which led Padmanaban and co-workers in 1982 to suggest the term rough ER–mitochondria (RERM) subfraction to describe a biochemical platform where cytochrome *c* oxidase is synthesized [6]. Yet, between the late 1950s and early 1980s, the association between the ER and mitochondria was mostly recognized by electron microscopists, who had determined with various model systems that up to 80% of mitochondria were in contact with the rough ER (rER) [7–9]. Electron microscopy tomography led to similar conclusions [10,11].

It was only during the late 1990s that Rizzuto and co-workers studied the MAM via live-cell imaging with ER and mitochondria-targeted probes [12]. Studies on lipid metabolism were the first to provide evidence that mitochondria could have functionally relevant contact sites with the secretory pathway [13]. However, this rather limited view of MAM functions changed dramatically at the turn of the millennium with the advent of localized calcium imaging demonstrating that the ER releases calcium in hotspots directed towards mitochondria [14,15]. Within mitochondria, calcium regulates cellular bioenergetics [16]. Today, we know that this organellar contact site is a critical intracellular signaling platform that determines cellular life and death and not just lipid homeostasis. Breakthrough papers published during the past decade have led to the insight that the MAM is characterized by a special proteome that regulates its formation

☆ This article is part of a Special Issue entitled: Mitochondrial dynamics and physiology.

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doi:10.1016/j.bbamcr.2012.04.013

and functions. A current challenge to the field is how human diseases, which are characterized by aberrant cellular metabolism or lifespan such as neurodegenerative diseases, diabetes or cancer, depend on malfunctioning MAM.

2. Lipid metabolism at the MAM

Studies on lipid synthesizing enzymes such fatty acid CoA ligase had shown already during the 1970s that both ER and mitochondria contain their activity [17]. Indeed, fatty acid CoA ligase 4 (FACL4), which mediates the ligation of fatty acids to coenzyme A (CoA) and is involved in triacylglycerol synthesis, is used today as one of the most reliable MAM marker proteins [18,19]. Likewise, early biochemical studies on triacylglycerol, phosphatidylcholine (PC) and phosphatidylethanolamine (PE) showed that the synthesis of these lipids requires enzymatic activity associated with both the ER and mitochondria, thus postulating a transport and transfer of lipids between the ER and mitochondria [13,20,21]. Subsequently, the enzymatic incorporation of serine into lipids was used to define a subregion of the ER (i.e., the MAM) [1]. This biochemical separation of ER membranes into mitochondria-associated membranes and purified ER then showed that the enzymatic activity of phosphatidylserine synthases 1 and 2 (PSS1, PSS2), two enzymes that catalyze the synthesis of the PC precursor phosphatidylserine (PS), was indeed associated with the MAM, not purified ER [22,23]. Mitochondrial phosphatidylserine decarboxylase was shown to utilize PS to produce phosphatidylethanolamine (PE) [24], in a distinct pathway to PE production on microsomes by ethanolamine phosphotransferase [25]. Since one of the final enzymes of PC synthesis, phosphatidylethanolamine methyltransferase 2 (PEMT2) [26], was again found to be restricted to the MAM [27], studies by the Vance laboratory nicely demonstrated that PC synthesis requires a tightly regulated lipid transfer back and forth between the ER and mitochondria, thus confirming earlier hypotheses [20]. In other words, the MAM provides a tight platform for lipid synthesis and lipid transfer between the ER and mitochondria. These findings are also consistent with the identity of several lipid metabolism enzymes as MAM markers: in addition to FACL4, acyl-coenzyme A:cholesterol acyltransferase-1 (ACAT1/SOAT1) is a MAM marker protein, since its enzymatic activity is among the most enriched on the MAM [22]. ACAT1 is a multimembrane-spanning enzyme that catalyzes the production of cholesterol esters, which are subsequently incorporated into lipid droplets [28].

Interestingly, the accumulation of lipid metabolism enzymes on the MAM could be the reason for the formation of a glycosphingolipid-enriched microdomain fraction at the MAM [29]. This observation and the identification of lipid rafts on the MAM associated with a special set of proteins [30,31] suggest that lipid synthesis and exchange at the MAM generate an ER subdomain with unique properties. More recent progress indicates that the MAM-localized lipid handling may also have a profound impact on mitochondrial metabolism, since yeast cells defective in PS biosynthesis become respiration-deficient [32] and mouse PS decarboxylase knockout cells show altered mitochondrial membrane dynamics [33]. The characterization of this functional link between lipid and mitochondrial metabolism will no doubt be one of the most exciting aspects of MAM research in the years to come.

3. ER–mitochondria calcium cycling at the MAM

Initially unconnected to this progress in the lipid field, studies on intracellular calcium signaling also reported that the ER and mitochondria could be functionally linked. During the 1980s, electron probe X-ray microanalysis had identified the ER as the cell's major calcium storage unit [34], not the mitochondria [35]. Since the import of calcium into mitochondria boosts the efficacy of mitochondrial enzymes [16], these findings raised the question of whether and how the two organelles exchange calcium in order to allow efficient mitochondrial metabolism [36].

Today, we know that cyclical calcium exchange between the two organelles is indeed essential for cell life and death [37]. Inside the ER, free calcium concentrations are close to extracellular calcium concentrations, but are orders of magnitude higher than cytosolic calcium concentrations (0.5 mM versus 100 nM). ER calcium determines the correct functioning of numerous ER enzymes involved in the manufacture of secretory proteins such as those used for N-glycosylation and oxidative protein folding like calnexin or calreticulin [38]. Although resting mitochondrial calcium concentrations are significantly lower in the range of hundreds of nM, calcium nonetheless influences their major biological mechanisms, including the production of ATP [39–41]. When mitochondria encounter cytosolic calcium concentrations of above micromolar levels, they can take up calcium to reach intramitochondrial calcium levels of micromolar ranges [42]. Such surges in intramitochondrial calcium activate numerous mitochondrial enzymes such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and even enzymes catalyzing oxidative phosphorylation [43]. The apposition of the ER with mitochondria is a prerequisite for calcium exchange between the ER and mitochondria, initiated by the massive release of calcium from the ER that follows the production of inositol-1,4,5-trisphosphate (IP3) [44], which binds to the IP3 receptor (IP3R) family proteins [45–47]. Vertebrates have three IP3R family members, but it is currently not clear how they are functionally distinct [48]. IP3R calcium release is maximal at cytosolic calcium concentrations of 100–300 nM [49] and cAMP-dependent protein kinase (PKA) phosphorylation promotes IP3R1 activity, whereas protein phosphatases 1 and 2A inhibit it [50]. Therefore, ER calcium release by IP3Rs is regulated by cytosolic calcium concentrations and their phosphorylation states. Since PKA is active under reducing, but not under oxidizing conditions in the cytosol [51], it might be promoting pro-metabolic calcium transfer from the ER into mitochondria dependent on the cytosolic redox state. Another ER calcium release mechanism is mediated by skeletal, cardiac and brain ryanodine receptors. These receptors localize to the sarcoplasmic reticulum of myocytes and the ER of neurons, respectively [52–54] and mediate calcium-induced calcium release in cardiac and skeletal muscle cells [55] and nitric oxide-induced calcium release in neurons [56].

After their intracellular release from the ER, free calcium ions cannot travel further than 100–500 nm before they typically encounter a calcium binding protein [57]. This high concentration of calcium binding proteins creates microdomains, termed calcium puffs in the proximity of ER calcium release channels that last for around 100 ms [58]. It also predicts that enzymes or organelles responsive to ER-released free calcium should be within a 500 nm radius of the ER tubules where IP3Rs release calcium [57]. This rule is expected to extend to mitochondria as well. Hence, in order to take up calcium vital for their enzymes, mitochondria should either be in this radius from the ER or should have the ability to approach these calcium puffs if needed [59]. Indeed, fluorescence microscopy with calcium-sensitive photo-proteins showed that mitochondrial movement is slowest when cytosolic calcium concentrations are high and come to a complete stop at >1 μM, as found for example in calcium puffs released by IP3Rs [60]. Calcium-sensitive probes attached to the outer mitochondrial membrane have further demonstrated that mitochondria specifically approach the ER, but not plasma membrane-proximal areas, where capacitive calcium influx occurs [61,62]. The direct implication of these findings is that it is through the delicate sensing of ER-released calcium microdomains that mitochondria determine their positioning within the cell. Moreover, these findings predict that the redox and calcium homeostasis of the ER not only determines ER protein folding, but also mitochondrial positioning as postulated by us in an earlier review [63].

Following the encounter of high cytosolic calcium concentrations, mitochondria take up calcium ions released from the ER. Interestingly, the identity of the protein responsible for this uptake of calcium into mitochondria has remained a mystery until 2011, when two elegant studies identified the long elusive mitochondrial calcium uniporter

(MCU) [64,65]. This protein channel with two transmembrane domains is relatively small at 40 kDa, but is part of a large molecular complex. Consistent with previous observations, the activity of this newly identified protein is sensitive to Ru360 and Ruthenium Red. When examined in live cells, these two compounds are able to block mitochondrial uptake of ER calcium that has been released through the IP3R [66]. Applying these compounds to live cells reveals the intricate relationship between the ER and mitochondria in intracellular calcium homeostasis. While mitochondria normally take up calcium from ER calcium release hotspots in a very short time frame following its release [12], in the presence of MCU inhibitors, the amplitude of ER-associated calcium puffs decreases [67]. These apparently contradictory findings can only be explained with a significant role of mitochondrial calcium uptake towards the regulation of IP3Rs. Since low or very high cytosolic calcium concentrations act to diminish IP3R opening and hence reduce ER calcium release [68], calcium released from the ER thus serves to autoregulate its release from this storage compartment. These findings also predict a central role of the extent of ER–mitochondria apposition, which equals MAM formation, in cytosolic calcium homeostasis. Thus, ER–mitochondria calcium signaling and exchange has to work interdependently to determine the calcium concentrations and the correct functioning of both the ER and mitochondria.

Once released from mitochondria through the Na^+/Ca^{2+} exchanger (NCLX) [69], calcium is efficiently taken up into the ER by calcium pumps of the sarco(endo)plasmic reticulum calcium ATPase (SERCA) family, which close the circle of intracellular calcium signaling between the ER and mitochondria [70]. The activity of SERCA calcium pumps is not only required for ER enzymes, it also determines the formation of calcium oscillating waves in the cytosol following the administration of IP3R agonists or the activation of G-protein coupled receptors [71]. The SERCA inhibitor thapsigargin slows cytosolic calcium waves and causes mitochondrial calcium overload that stems from high cytosolic calcium concentrations [72]. This condition ultimately provokes the irreversible opening of IP3Rs through the binding of mitochondrial cytochrome *c* at the MAM, triggering apoptosis. Thus the MAM can also accommodate a massive transfer of calcium from the ER to mitochondria to promote cell death [73] and therefore not only determines ER–mitochondria calcium signaling, but also the speed of apoptosis onset [74,75].

4. Lipid metabolism markers of the MAM

It is only in this current decade that the characterization of the proteome of the MAM has started in earnest [76]. So far, proteomic studies on the MAM have been a huge challenge for the field and future proteomic approaches will have to ensure that the correct membrane domains are isolated. The purity of MAM preparations is often low due to contaminations with mitochondria and other domains of the ER. Moreover, the MAM itself is to some extent a moving target. For example, a number of recently published studies have demonstrated that the extent and the composition of the MAM changes upon cell stress, in particular ER stress. Under this condition, the extent of the MAM increases [77], because the ER and mitochondria move closer to each other, likely causing an alteration of the MAM proteome [78]. Conversely, some MAM proteins like Ero1α leave the MAM when cells are stressed [79]. Cytosolic proteins that regulate the enrichment of MAM proteins also show different localization and interactions dependent on cell stress [75]. Therefore, proteomic studies have to take into account controlled cellular homeostasis. Nevertheless, already today some statements and predictions can be made about the composition of the MAM (Fig. 1, Table 1).

Historically, the first set of proteins identified on the MAM contained proteins of ER-associated lipid metabolism such as PEMT2 and PSS1/2 [23,27]. Another MAM protein is acyl-CoA:diacylglycerol acyltransferase 2 (DGAT2), which targets to the MAM, unlike DGAT1 [80]. Whereas the MAM enrichment mechanism is not known for PEMT2 and PSS1/2, in the case of DGAT2 it is a 5 amino acid mitochondrial-targeting signal that is necessary for enrichment on the MAM. This targeting signal consists of basic amino acid residues found close to the first transmembrane domain of DGAT2. Amongst the most reliable MAM markers known today are ACAT1/SOAT1 and ACS4/FACL4 [18,19,28]. However, ACS4/FACL4 also localizes to peroxisomes, which mature from ER membranes [81–83]. It is currently not known whether ACAT1/SOAT1 also resides outside of the MAM. Plasmid-based expression of these marker proteins has led to mixed results: whereas myc-tagged PSS1 is restricted to the MAM [23], green fluorescent protein (GFP)-tagged PSS1 is also found on other domains of the ER [84]. This discrepancy has so far hampered live cell imaging efforts, because GFP-tagging might mask targeting information required for sorting into the MAM or might lead to oligomerization that results in mistargeting within the ER [85].

5. Calcium handling proteins of the MAM

The second large group of proteins localized to the MAM comprises calcium-handling proteins. Early immunofluorescence studies in neuronal cells have detected SERCA and IP3R2 on domains of the ER that are in close proximity of mitochondria [86,87]. However, the distribution of IP3Rs to domains of the ER is wider than for SERCA2b in PC12 cells, suggesting that IP3R might lack ER domain targeting information [88]. Nevertheless, even SERCA2b is not restricted to the MAM in HeLa cells [89]. Consistent with this impression, quantitative biochemical approaches have shown that while IP3Rs are certainly present on the MAM, antibodies against all three IP3R isoforms see these calcium channels predominantly on microsomes, which contain the rER [77,90], but also on the nuclear envelope [91]. When narrowing down to specific isoforms, IP3R1 and IP3R3 show a distinct intracellular localization [92]. IP3R1 appears to be found on all domains of the ER [93–95], whereas IP3R3 is MAM-enriched in CHO [96,97], but not in mouse embryonic fibroblasts [98] or HeLa cells [89]. IP3R2 has been reported to cluster upon ionomycin or thapsigargin treatment [206]. Despite these findings, it is however the IP3R3 form that preferentially transmits calcium signals from the ER to mitochondria [99]. How can we explain this apparent contradiction? If IP3R3-mediated calcium release occurs on the MAM, but IP3R3 is not MAM-restricted, these findings suggest that *active* IP3R3 is specifically restricted to the MAM. Thus, despite the involvement of calcium channels and pumps in direct calcium transfer from the ER to mitochondria on the MAM [59], the highly localized activity of IP3Rs and SERCA pumps could be regulated by their post-translational modifications or protein–protein interactions (see Section 6), leading to an ER-domain-specific activation or inactivation of the channels and pumps. For example, this idea is partially supported by the localization of active, PKA-phosphorylated IP3R1 to dendrites in neurons, whereas the non-phosphorylated form is found in the cell body [100].

Both IP3Rs and SERCA interact with numerous regulatory proteins, which could also determine the domain-specific activation of these proteins. Varying amounts of these regulatory proteins have been detected on the MAM, further suggesting that MAM calcium signaling might be predominantly determined by the presence of regulatory proteins on the MAM rather than a preferred presence of calcium-handling proteins there. One of the best-characterized calcium regulatory proteins is the sigma-1 receptor [101]. This transmembrane protein interacts with ion channels at the plasma membrane and with the IP3R3 on the MAM, where it exerts a chaperone activity [96]. Normally, sigma-1 receptors associate with the chaperone BiP/GRP78, but under conditions of low ER calcium or upon the binding of agonists (e.g., pentazocine), they bind to IP3R3 and prevent ubiquitin-mediated degradation of this calcium channel. The

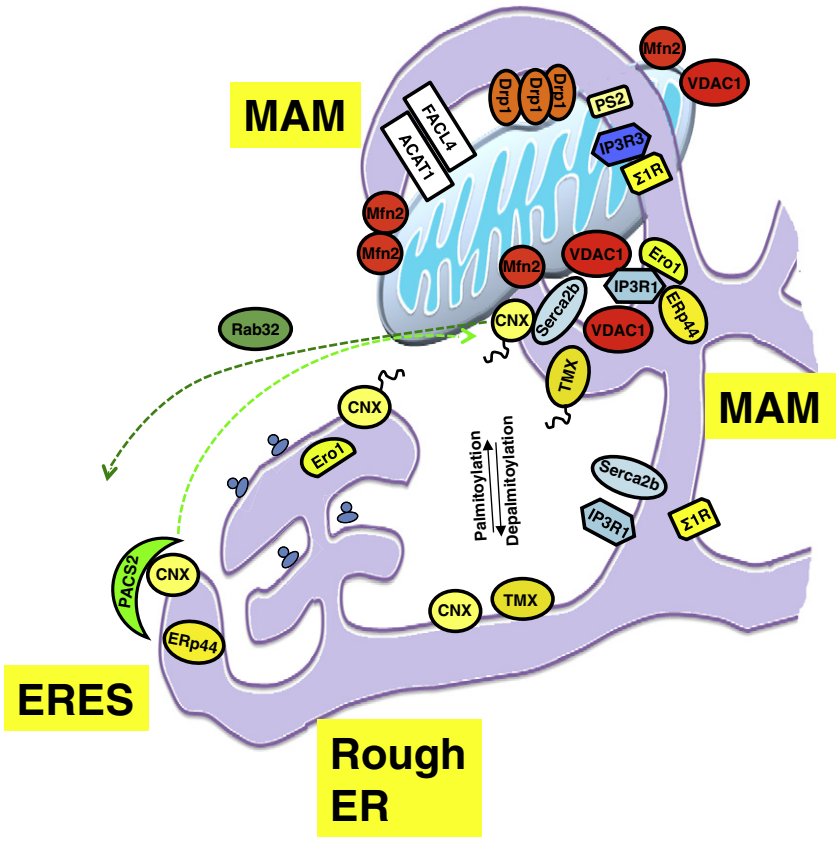

Fig. 1. Diagram of mammalian MAM-enriched proteins, as summarized in Table 1. Only *bona fide* mammalian MAM proteins are represented, see Table 1. The MAM is a hub for lipid metabolism (white; top portion of MAM), mitochondrial fission (orange; indicated by the Drp1 oligomers) and ER chaperones and oxidoreductases (yellow; bottom portion of MAM). Enrichment of MAM proteins to the vicinity of mitochondria is regulated by lipid modification (palmitoylation) and by cytosolic sorting proteins (green; PACS-2, Rab32). MAM tethering involves mitofusin-2, GRP75 (not shown) and VDAC1 (red). Calcium handling proteins such as SERCA2b, IP3R1 and IP3R3 are found on the MAM (blue), but do not appear specifically enriched here. Details and references are found in the text.

consequence of sigma-1 receptor binding to IP3R3 is a boost of calcium transfer from the ER to mitochondria [96]. The localization of the sigma-1 receptor to the MAM depends on the lipid composition of the ER. The depletion of cellular cholesterol leads to relocation of sigma-1 receptors to other domains of the ER, suggesting that detergent-resistant membranes are involved in the MAM targeting of this protein [102]. Similar to the sigma-1 receptor, a portion of the promyelocytic leukemia (PML) tumor suppressor protein associates with IP3Rs at the MAM [98]. PML physically associates with IP3R3 and promotes its calcium release activity by allowing the binding of protein phosphatase 2a (PP2a) to the IP3R3, which unlike for IP3R1 [50] results in increased opening of the IP3R3 and opposes the activity of the kinase Akt [103].

Not much information is currently available on the ER domain localization pattern of RyR or calcium release channels of the transient receptor potential cation (TRPC) family. In cardiomyocytes, RyR localize to the sarcoplasmic reticulum [52] in clusters that are found on the mitochondria-distal face of the sarcoplasmic reticulum, corresponding to the location of dyads [91,104]. Also in neurons, calcium release from RyRs occurs from both the rough and the smooth ER [105].

6. Oxidoreductases and chaperones of the MAM

An important group of MAM proteins are ER protein folding chaperones and oxidoreductases [63]. Amongst the interactors of the IP3Rs is the oxidoreductase ERp44, a thioredoxin-related luminal protein of the ER and the Golgi complex that retains proteins in the ER if they expose unpaired cysteines, but also promotes immunoglobulin polymerization [106,107]. ERp44 interacts with IP3R1 most strongly under reducing conditions and when the ER calcium content is low [108]. The redox-dependent interaction of ERp44 with IP3R1 inhibits ER calcium release, suggesting this interaction is a protective mechanism that increases ER calcium concentrations under ER stress and suboptimal ER folding conditions. That this mechanism is directly tied to the status of oxidative protein folding is evidenced by the ability of another oxidoreductase, Ero1α, to modulate it [93]. Ero1α is an enzyme that recharges protein disulfide isomerase (PDI), one of the major catalysts of disulfide bond formation [109]. Ero1α localizes to the MAM under resting conditions, but relocates to other domains of the ER and becomes secreted, when cells are in a reducing or hypoxic environment [79]. Ero1α can interact not only with ERp44, an interaction that helps retain Ero1α in the ER [110], but also with IP3R1, resulting in the oxidization of this calcium channel [93,111]. The interaction of Ero1α with oxidized IP3R1 reduces the ER calcium content during resting conditions and during the onset of apoptosis. ER stress and hypoxia activate the transcription factor CHOP that induces Ero1α, which oxidizes IP3R1 and removes ERp44 from IP3R1, thus leading to IP3R1 opening [93,111]. Likewise, the MAM targeting of Ero1α likely determines the extent of MAM calcium handling. We will discuss the medical implications of these findings in Section 10.

Another ER folding chaperone that modulates ER calcium signaling and resides on the MAM is calnexin. Calnexin is a lectin that folds newly synthesized glycoproteins and can interact with ribosomes [112,113] as well as with the oxidoreductase ERp57 [114]. A closely related ER folding assistant involved in the regulation of ER calcium signaling is calreticulin [115,116], but like ERp57, this luminal protein is not enriched on the MAM [79]. In contrast to calreticulin, the localization mechanisms of calnexin to individual domains of the ER are well characterized. Interaction with ribosomes requires calnexin phosphorylation by MAPK and protein kinase CK2

Table 1
MAM proteins, their degree of MAM enrichment and remarks. Summary of the most important proteins of this review. Proteins are grouped according to their function. Extent of MAM enrichment is noted with references where available. Additional notes summarizing information on interacting proteins are indicated on the right, additional references and details are found in the text.

MAM function	Proteins involved	MAM enrichment	Notes, interactors
Lipid synthesis	FACL4	High [18,75]	Ligates fatty acids onto coenzyme A; also found on peroxisomes
	ACAT1	High [22]	Ubiquitous
	PSS1/2	High [23]	Not ubiquitous, synthesize phosphatidylserine
	PEMT2	High [27]	Hepatocytes only, methylates phosphatidylethanolamine; also found on lipid droplets
	DGAT2	Medium–high [80]	Uses 5 amino acid mitochondrial targeting signal to become enriched on MAM
ER calcium release and uptake	IP3R1	Low [93,95]	Interacts with ERp44 (inhibitor) and Ero1α (activator) as well as VDAC1
	IP3R3	Low–medium [89,96,98]	Main transmitter of ER–mitochondria calcium signals Variable localization in non-neuronal cells? Interacts with PML and sigma-1 receptor (activators)
	SERCA2b	Sometimes MAM enriched [89]	Ubiquitous, interacts with calnexin (inhibitor)
Mitochondrial calcium release and uptake	MCU	?	Very little MAM-relevant information available at this moment
	NCLX	?	
ER calcium regulation	ERp44	Low [79]	Mostly found on ERES
	Ero1α	High [79]	MAM localization is redox-dependent
	Calnexin	Medium–high [120]	MAM localization is ER stress-regulated; enriched on MAM with PACS-2, extracted from MAM with Rab32; when on MAM palmitoylated
	Presenilin-2	High [122]	
	Sigma-1 receptor	Medium–high [96,102]	Interacts with IP3R3; MAM targeting dependent on lipid rafts
Enrichment and removal of MAM proteins	PACS-2	Low [75]	Can shift onto MAM under cell stress
	Rab32	Medium [121]	Also found on mitochondria
MAM tethering	VDAC1	Low [95]	Forms a tether with GRP75 and IP3R1; mostly found on mitochondria
	Mitofusin-2	Medium [74]	Best characterized MAM tether in mammalian systems; mostly found on mitochondria; interacts with TpMs (inhibitor)
	BAP31	?	Interacts physically with Fis1 and functionally with PACS-2
	ERMES	High [150]	Complex so far only detected in yeast (composed of Mmm1p, Mdm12p, Mdm10p, Mdm34p)
Mitochondrial movement	Miro	?	Connection with MAM unclear
	Gem1p	?	Connection with MAM and ERMES unclear
Mitochondrial morphology	Drp1	?	Might be highly MAM-enriched when fission is promoted
Viral proteins	UL37	Low–medium [201]	Can transfer from ER onto mitochondria
	Vpr	Low [204]	Accumulates on MAM when mitochondrial fission is blocked

[112]. However, calnexin, together with ERp57, also interacts with SERCA2b as shown in *Xenopus* oocytes [116,117]. This interaction requires the phosphorylation of the cytosolic domain of calnexin by ERK and PKC kinases [117,118] and reduces the activity of SERCA2b. Interestingly, while calnexin mediates protein folding on the rER, it localizes predominantly to the smooth ER [119] and within this structure to the MAM [120]. Enrichment of calnexin on the MAM depends on the interaction with cytosolic phosphofurin-acidic cluster sorting protein 2 (PACS-2), which binds to non-phosphorylated calnexin on a cytosolic cluster of acidic amino acids [120]. In addition, calnexin MAM localization also depends on the activity of the ER Rab protein Rab32 [121]. Moreover, calnexin needs to be palmitoylated in order to show MAM enrichment, again suggesting that special lipid properties of the MAM determine MAM function and targeting [89]. Together, these findings suggest that calnexin utilizes multiple mechanisms to target to distinct domains of the ER, depending on whether it acts as a protein folding chaperone or a modulator of ER calcium signaling. Future studies will have to determine how ER homeostasis decides between these functions of calnexin and regulates its intra-ER targeting.

7. Other proteins of the MAM

Recent publications have led to the exciting finding that presenilin-2 (PS2) is a MAM protein [122]. PS2, together with presenilin-1, is a part of the γ-secretase complex (together with APH1, nicastrin and PEN2) that is required for the cleavage of the amyloid β-precursor protein (βAPP) [123]. Distinct from presenilin-1 however, the expression level of PS2 determines the exchange of calcium between the ER and mitochondria: in cells over-expressing PS2, mitochondrial calcium uptake following ER calcium release is increased, whereas cells with low levels of PS2 show reduced ER–mitochondria calcium transfer [124]. In addition to modulating mitochondrial oxygen consumption and mitochondrial membrane potential [125], these observations have far-reaching consequences that might form a molecular basis for Alzheimer's disease. The expression of disease-associated PS2 mutants increases the ER–mitochondria interaction so much that it eventually results in mitochondrial calcium overload and, hence, apoptosis [126]. Like calnexin, PS2 exhibits a cytosolic acidic cluster that is connected to a protein kinase CK2 site, which is the consensus PACS-2 interaction motif, thus raising the interesting possibility that PACS-2 regulates PS2 localization like it does in the case of calnexin [127].

The studies on the localization of the autocrine motility factor receptor (AMFR) suggest that different kinds of MAM might exist. This receptor for AMF/phosphoglucose isomerase targets to a subdomain of the smooth ER, which extends from the rER and is in close contact with mitochondria [128]. Interestingly, this domain does not label for calnexin, a MAM-enriched chaperone, suggesting that calnexin and AMFR could target to two distinct kinds of MAM [129]. Given the peripheral localization of AMFR [128], we are speculating that these different kinds of MAM might regulate the functioning of perinuclear and peripheral mitochondria. Nevertheless, AMFR is also implicated in ER calcium homeostasis, since Cos7 cells with AMFR levels knocked down show a reduced ability to release calcium through the IP3R [130].

In summary, recent progress has dramatically increased the characterization of the MAM proteome and has led to a better understanding of the function of the MAM. Research from various laboratories has identified MAM-enriched lipid metabolism enzymes and MAM proteins that regulate calcium handling. Surprisingly, the evidence that calcium-handling proteins themselves are MAM-enriched is currently far from convincing. Important questions that the field needs to answer are whether active calcium channels and pumps target to the MAM and whether by itself, the clustering of active calcium channels and pumps could act as a MAM nucleation event. Such a hypothesis is not unfounded, given the ability of calcium puffs to attract

mitochondria. In such a scenario, calcium channel pump accumulations on the MAM would then serve to dissolve the MAM structure. For the moment, this remains an interesting hypothesis that awaits testing.

8. Physical connections between the ER and mitochondria in mammalian cells

As recently as 5 years ago, the only information available on the identity of MAM tethers was that these tethers should be of proteinaceous nature, since phospholipid import into mitochondria decreases upon incubation of the mitochondria and the MAM with proteinase K in yeast [131]. Moreover, in mammalian cells ER–mitochondria separation also disrupts calcium transfer [77] and causes ER stress [75,132]. In addition to protein tethers, another requirement for the maintenance of the MAM appears to be the correct retention within the ER of a subset of transmembrane proteins with cytosolic acidic cluster motifs recognized by PACS-2 [75]. Accordingly, cells with low levels of PACS-2 show a visible detachment of mitochondria from the ER and a reduced ability to release calcium upon IP3R stimulation [75]. However, it is currently unclear what is the cause and effect of these observations.

Very recent research has demonstrated that MAM protein tether pairing at the ER and mitochondria has to be a reversible, regulated mechanism, since ER stress caused by the accumulation of unfolded proteins increases MAM tethering that manifests itself by an increased overlap of ER and mitochondria under this condition [77,78]. The purpose of this increased apposition could be the promotion of mitochondrial metabolism, likely to increase energy import into the ER for ER oxidative protein folding, thus alleviating the accumulation of unfolded proteins in the ER [78]. This promotion of mitochondrial metabolism requires calcium release from the ER through IP3Rs [16]. Together, these functional links nicely illustrate the symbiotic relationship between the ER and mitochondria.

Interestingly, the same mechanism is also central to apoptosis progression, since cytochrome *c* released from mitochondria following a calcium overload can bind to IP3R1 [73]. Cell death mediated by Fas ligand binding to hepatocytes, HeLa cells and Jurkat T lymphoma [133,134] heavily relies on this protein–protein interaction at the MAM, thus highlighting the importance of MAM tethers not only for mitochondrial metabolism, but also for programmed cell death.

Starting in 2006, a rapid succession of breakthrough papers has led to the identification of several ER–mitochondria tethering complexes, both in yeast and mammalian cells. One of these complexes is based on the interaction between the voltage-dependent anion channel 1 (VDAC1) and the outer mitochondrial membrane chaperone GRP75 [95]. The interaction of mitochondrial VDAC1 with GRP75 strengthens the functional interaction between the ER and mitochondria by forming a ternary bridging complex that also comprises IP3R1 on the ER, thus optimizing calcium transfer from IP3Rs to mitochondria [95]. Accordingly, GRP75 knockdown reduces calcium transfer from the ER to mitochondria. VDAC family members localize to the outer mitochondrial membrane [135]. Through their functions as channels for, among others, ATP [136], ions and anions [137], and as anchors for metabolic enzymes (e.g., hexokinase [138]) and Bcl2 family proteins [135], VDAC family proteins act as central regulators of mitochondrial metabolism. Interestingly, in particular in neurons, VDAC1 also localizes to the ER on the membranes that constitute the MAM (V. Shoshan-Barmatz, personal communication) [139]. The same observation was made in HeLa cells [89]. At the MAM, VDAC family proteins have been suggested to serve as an ATP conduit, which would provide energy for ongoing protein folding inside the ER [140]. Such a function might even extend into apoptotic calcium transfer from the ER to mitochondria involving IP3Rs [141], but whether this mechanism cooperates with previously demonstrated ones involving cytochrome *c* remains to be demonstrated.

VDAC is not an isolated case of a mitochondrial protein that also localizes to the ER and is involved in ER–mitochondria tethering. Mitofusin-2 is a dynamin-related GTPase that is implicated in mitochondrial docking and fusion [74,142], but is also found on the MAM, as shown by the Scorrano laboratory in 2008 [74]. ER–mitochondria juxtaposition and calcium signaling on the MAM also depends on mitofusin-2 [74]. Moreover, in one of the most intriguing studies on the metabolic function of the MAM to date, it was recently shown that mitofusin-2 ablation in the liver causes ER stress that subsequently results in glucose intolerance and impaired insulin signaling [132]. MAM-localized mitofusin-2 also interacts with trichoplein/mitostatin (TpMs). This keratin-binding protein inhibits mitofusin-2 and blocks mitochondrial fusion while loosening MAM contacts when over-expressed [143].

Another MAM regulatory protein is the B-cell receptor associated protein of 31 kDa (BAP31). This protein with three transmembrane spanning domains acts as an accessory ER protein folding chaperone for substrates such as the major histocompatibility complex class I or immunoglobulins [144–146]. However, BAP31 is also an important regulator of ER–mitochondria crosstalk. Apoptosis induction leads to the interaction of caspase-8 with BAP31, creating a proteolytic fragment of BAP31 that promotes calcium release from the ER [147]. The interaction of caspase-8 with BAP31 could depend on the formation of a complex with the mitochondrial fission protein Fis1, which could result in a MAM-localized apoptotic platform [148]. The sequence of events in this cascade remains to be studied however, since cleavage of BAP31 appears to precede ER–mitochondria calcium transfer and apoptosis onset [147]. In addition, BAP31 also interacts with calnexin, which regulates stress-dependent cleavage of BAP31 by caspase-8 [149]. Interestingly, knockdown of the MAM sorting protein PACS-2 not only leads to the removal of calnexin from the MAM, but also to BAP31 cleavage and MAM disruption [75,120]. Together, these studies demonstrate a regulatory role of BAP31 in ER–mitochondria crosstalk, but also suggest that further research is needed to understand the sequence of events and whether interactions between BAP31 and its many interactors are a requirement for MAM signaling mechanisms.

9. The yeast ERMES complex

Following this progress on the identification of MAM tethers in mammalian cells, Kornmann et al. provided an important contribution with the identification of the ER–mitochondria encounter structure (ERMES) in an elegantly conceived yeast genetic screen [150]. ERMES comprises the integral ER membrane protein Mmm1p, the peripheral ER membrane protein Mdm12p, and the two mitochondrial outer membrane proteins Mdm10p and Mdm34p [150,151]. Previously, components of ERMES had been suggested to fulfill other roles at mitochondria. For instance, Mdm10p, Mdm12p, and Mmm1p had been implicated in mitochondrial connections to the actin cytoskeleton and in mitochondrial movement [151]. Apparently consistent with such hypotheses, the yeast calcium-binding GTPase Gem1p, which is related to mitochondrial Rho proteins (Miro), had also been identified as peripherally associated with the ERMES [152,153]. Miro GTPases indeed function as calcium-dependent sensors to control mitochondrial motility in mammalian cells and seemed thus to back up the hypothesis of a role of ERMES in mitochondrial movement [154,155]. Similarly, it has been speculated that ERMES could be part of higher protein complexes that connect the control of ER and mitochondrial metabolism to the structure and maintenance of mitochondria [156]. However, while a role of ERMES in mitochondrial morphology and tethering of the ER to mitochondria remains undisputed, a recent publication has shed serious doubts on some early findings and in particular on the role of Gem1p in the regulation of ERMES [157]. In this detailed study by the Shaw, Rapoport and Voelker laboratories, ERMES may act as a stable tether between the ER and mitochondria

that is not important for ER–mitochondria phosphatidylinositol transfer, mitochondrial movement or mitochondrial interaction with the actin cytoskeleton. Moreover, Gem1p was found to be dispensable for the formation of ERMES. At the moment therefore, these findings suggest the existence of additional ER–mitochondria tethering mechanisms in yeast as well as a need for further research to understand the regulation and formation of ERMES. One further caveat of the findings in yeast is that we currently do not know which mammalian proteins fulfill the function of the ERMES complex and what the role of the known mammalian tethers is for the yeast MAM. Interestingly however, a proteomic analysis of yeast MAM has confirmed the presence of some BiP/GRP78 and VDAC/porin within yeast MAM [153], consistent with findings from mammalian cells [89,95,96,139] and suggesting that indeed, MAM structure and composition in yeast and mammalian cells might be more similar than currently known.

10. The MAM in health and disease

The vast implications of calcium signaling on various intracellular signaling mechanisms demonstrate the importance of the MAM for metabolism and cellular lifespan. Not surprisingly, the MAM has been proposed as a site that is affected in neurodegenerative diseases [158]. The role of the MAM in diabetes is an exciting emerging area of research [132,159]. Proteins implicated in cancer like PML [103], in the viral manipulation of cellular metabolism [160] and in inflammation [161,162] have been detected on the MAM as well, evidencing the huge potential of future studies in the field to further our understanding of human disease. We will discuss selected mechanisms and diseases in this chapter.

Neuronal cells require very large amounts of energy for their activities and rely almost exclusively on mitochondria as a provider, in particular in axons and dendrites [163]. Thus, the distribution and morphology of mitochondria is a critical determinant of neuronal survival [164,165]. The role of the MAM for neuronal survival is based on the presence of smooth or rough ER all the way throughout axons and dendrites [166]. Consistent with this, a number of ER structural proteins can give rise to neuronal defects if mutated. Notably, reticulon-4, also known as neurite outgrowth inhibitor (Nogo), promotes ER tubulation [167], but might also influence the calcium-dependent apposition between the ER and mitochondria [168]. Such a function could potentially be assigned to many enzymes regulating ER tubulation, such as receptor expression enhancing protein 1 (REEP1) that regulates ER network formation, but also mitochondrial membrane dynamics [169,170]. Interestingly, REEP1 is a genetic cause for hereditary spastic paraplegia [171], which is reminiscent of the well known role of the microtubule severing protein spastin in both the connection of ER tubules to the cytoskeleton [170], but also the trafficking of mitochondria along axons [172,173].

The dynamic membrane contacts at the MAM could require the calcium-dependent Ras GTPases Miro-1 and Miro-2 that promote mitochondrial clustering when active by forming a link between mitochondria and microtubules [174] and kinesin heavy chain (KIF5) [154]. These calcium-dependent interactions may provide a mechanism behind the ability of mitochondria to move towards calcium puffs released by IP3Rs [60]. The Miro protein complex also interacts with mitofusin-2 [175], which is also essential for the transport of mitochondria along the axons [175]. Mitofusin-2 mutations lead to Charcot Marie Tooth type 2A disease, a peripheral neuropathy [176,177], wherein the longest neurons in patients die [178]. Consistent with the potential involvement of the MAM, it has been proposed that a mitochondrial transport defect leads to the disease [176]. This defect could stem from an inability of mitofusin-2 mutated neurons to form the MAM or from an inability of mitofusin-2 mutants to interact with kinesin [179].

Another neurodegenerative disease tied to the MAM is Alzheimer's disease [158]. Alzheimer's disease-associated mutations in PS2 lead to reduced ER calcium content and even further increased ER–mitochondria calcium transfer when compared to wild type overexpression [126]. The increased ER–mitochondria calcium communication has dramatic consequences in cells with mutant PS2. These cells show markedly increased apoptosis susceptibility, which could explain the aberrant neurodegeneration in Alzheimer's patients, thus leading to the provocative proposal by Eric Schon that Alzheimer's is actually a disease of a malfunctioning MAM [124,158]. Consistent with a role of the MAM for maintaining neuronal function, PS2 is needed for the normal oxygen consumption and mitochondrial membrane potential of neurons [125].

Another important connection between the MAM and neuronal function is based on dynamin-related protein 1 (Drp1). Recently, ER tubules have been suggested as the means by which Drp1 oligomers constrict mitochondrial structures [180]. The intracellular localization of Drp1 has remained disputed over the years with reports ranging from ER [181] to mitochondria [182]. Its association with the MAM could potentially reconcile these discrepancies, but such a formal demonstration currently awaits publication. That the MAM plays an important role for Drp1 is evidenced by its relationship with the ER–mitochondria-associated Rab32: our laboratory has shown that inactivation of Rab32 mislocalizes and inactivates Drp1 [121]. Multiple links exist between Drp1 and neurodegeneration [183]. For example, Alzheimer's patient brains exhibit increased mitochondrial fission activity and express higher levels of Drp1 in an Aβ-dependent manner [184,185]. In Parkinson's disease, loss of function mutations in the PTEN-induced putative kinase 1 (PINK1) and in parkin lead to increased mitochondrial fragmentation catalyzed by Drp1 that also coincides with an arrest of mitochondrial motility [186,187]. These effects are based on the kinase activity of PINK1 and a ubiquitin ligase activity of parkin [188], which lead to altered phosphorylation and hence activity of Drp1 [189,190]. Parkin is also able to ubiquitinate Drp1 directly, thus mediating its degradation [191]. Since mitofusin-2 and Drp1 are critically involved in MAM function and also localize to ER–mitochondria contact sites, the sum of these findings amply demonstrates the prominent role of the MAM in the etiology of numerous neurodegenerative diseases.

The past decade has also seen the association of a number of MAM proteins with cancer and tumorigenesis. For example, the cytosolic sorting protein PACS-2 that maintains MAM integrity and ER–mitochondria calcium exchange is mutated in as much as 40% of sporadic colorectal cancer biopsies and could thus act as a tumor suppressor [192]. However, the maintenance of the MAM and its calcium signaling platform is not a clear hallmark of cancer, since the tumor suppressor PML actually promotes the opposite: PML interacts with IP3R3, leading to its hyper-phosphorylation, which results in reduced ER–mitochondria calcium flux and apoptosis resistance [103]. Similarly, the suspected tumor suppressor trichoplein/mitostatin (TpMs) inhibits mitofusin-2 and hence MAM formation, but is downregulated or mutated in a number of types of cancer [193,194]. Thus, while proteins regulating the MAM are clearly associated with cancer, future research will have to elucidate which functional aspect of the MAM is most critical for tumorigenesis: apoptosis onset or the maintenance of cancer cell metabolism.

Another important group of MAM regulatory proteins are chaperones and oxidoreductases of the ER such as BiP/GRP78, ERp44, Ero1α, and calnexin [93,96,108,111,117,120]. All of these are central players in ER–mitochondria calcium flux [63]. Hypoxic cancer tissue shows HIF1α-dependent upregulation of Ero1α, which leads to tumor cell proliferation [195]. Given its redox-dependent relationship with ERp44 [106,108], high expression of Ero1α in hypoxic cancer tissue could thus result in altered IP3R calcium signaling. Future research will have to determine whether this results in increased activity of IP3R [93], or simply in increased secretion of Ero1α [79]. In mouse models, it has been shown that loss of Ero1α function leads to reduced peak amplitude of cardiomyocyte calcium

transients, resulting in a partial resistance to progressive heart failure [196]. Thus, increased Ero1α expression levels could be associated with overproliferation resulting in tumors, whereas heart disease progression might also be characterized by an increase of Ero1α expression.

This latter aspect is also important for the MAM-associated regulation of calcium signaling by SERCA. The cellular redox state plays an important role in the regulation of SERCA activity by promoting multiple, redox-dependent modifications on Cys674, which is present in both SERCA2a and SERCA2b. Whereas mild oxidation leads to the glutathionylation of Cys674 and increases pump activity [197], chronic oxidation oxidizes other cysteines and causes irreversible sulfonation of Cys674 that results in a complete stop of calcium pumping [198]. Recently it has been shown that oxidative inhibition of SERCA by exposure of a modest oxidative stress (100 μM H_2O_2) in cardiac myocytes causes a contractile phenotype characterized by reduced contractile amplitude, reduced amplitude of the intracellular calcium transient, and depletion of the sarcoplasmic reticulum calcium [199]. Conversely, nitroxyl and peroxynitrite increase calcium cycling in cardiac myocytes via S-glutathionylation of SERCA and its subsequent activation [197]. These results indicate how cellular redox and redox-sensitive enzymes could directly modulate the calcium signaling function of the MAM.

In addition to modulating MAM calcium signaling, the Tschopp laboratory has recently made the exciting discovery that reactive oxygen species (ROS) lead to the activation of NOD-like receptor protein 3 (NLRP3) inflammasomes [162]. This activation coincides with the shift of thioredoxin-interacting protein (TXNIP) from cytosolic thioredoxin 1 to the NLRP3 inflammasome on the MAM. Increased ROS production inside mitochondria due to extra- or intracellular stress triggers is a prerequisite for this observation [161]. Interestingly, the MAM structural component VDAC is integral to this response, since RNAi-mediated VDAC1/2 knockdown abrogates inflammasome formation in response to monosodium urate, alum or nigericin. Similar to apoptosome formation that requires the release of mitochondrial cytochrome *c*, ROS-triggered inflammasome activation might require the release of mitochondrial DNA, providing an additional potential role for the MAM [200].

Given these important roles of the MAM for calcium signaling, apoptosis and inflammasome activation, it comes as no surprise that numerous viral proteins target this structure. One prominent and well-described example is the human cytomegalovirus glycoprotein UL37 exon 1 [201]. Unless this protein is expressed, cytomegaloviruses induce apoptosis of infected cells [202]. This glycoprotein targets to the MAM with two mitochondrial targeting signals [203] and is able to reduce ER calcium content, possibly by increasing the targeting of GRP75 to the VDAC/IP3R/GRP75 ternary complex [201] or by modulating the amount of calcium-regulating chaperones and oxidoreductases such as BiP on the MAM [76]. The MAM also houses the cytosolic pathogen recognition receptor RIG-1 that triggers an immunity signaling cascade upon viral infection [84]. More recently, HIV-1 Vpr has been suggested to disrupt the MAM by reducing mitofusin-2 and Drp1 protein levels [204]. Given the complexity of MAM functions that promote cellular metabolism, but also apoptosis, numerous reasons exist for MAM interference by viral proteins. Future research in this exciting field will have to address which aspect is targeted for individual examples.

11. Conclusions

The ER forms a superorganelle with distinct domains performing specific functions [205]. Compared to the rER, the MAM is still not the best defined or characterized ER subdomain. However, during the past decade, a series of important papers has been published that demonstrates a central role of the MAM in the regulation of cellular metabolism [16,78], apoptosis progression [73], intracellular calcium homeostasis [74], the maintenance of ER redox conditions [75] and mitochondrial membrane dynamics [74,180]. After the initial discovery of lipid synthesizing enzymes on the MAM [1], we now know that the MAM proteome is much more complex and comprises tethering proteins that can localize to both the ER and mitochondria [74,95], ER chaperones and oxidoreductases that regulate its function [79,89,96] as well as ER calcium channels and pumps. Importantly, we start to understand that some of these proteins including IP3R and SERCA are only enriched on the MAM to some extent in a temporary and cell-stress dependent manner. Therefore, future research will have to describe more MAM enrichment mechanisms along the lines of the cytosolic sorting proteins PACS-2 and Rab32. Areas of controversy in the field currently comprise the role of the MAM in mitochondrial membrane dynamics (e.g., Drp1, BAP31), the identity and function of MAM tethers (e.g., ERMES) and the extent to which MAM proteins target to this domain, in particular calcium handling proteins and GFP fusion proteins. Also, although so far not demonstrated, a tempting possibility exists that the MAM could accommodate a partial fusion and protein exchange between ER and mitochondrial membranes. No doubt the coming 20 years of MAM research will prove as exciting as the first 20 and will give important insight into the biogenesis of numerous important human diseases, including neurodegeneration and cancer.

Acknowledgements

We thank Jean Vance, Janet Shaw and Emily Lynes for helpful discussions and critical reading of the manuscript. Research in the Simmen lab is supported by Alberta Cancer Foundation grant #25018, CCSRI grant 2010–700306, NSERC grant 386757–2010 and Alberta Innovates Health Solutions scholarship 200500396. Arun Raturi was supported by an Alberta Innovates: Health Solutions postdoctoral fellowship.

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