Seminars in Cell and Developmental Biology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Cell and Developmental Biology

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

The Mitochondrial-associated ER membrane (MAM) compartment and its dysregulation in Amyotrophic Lateral Sclerosis (ALS)

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ARTICLE INFO

Keywords:
ALS
MAM dysfunction
Lipid homeostasis

ABSTRACT

The endoplasmic reticulum (ER) and mitochondria connect at multiple contact sites to form a unique cellular compartment, termed the 'mitochondria-associated ER membranes' (MAMs). **MAMs are hubs for signalling pathways that regulate cellular homeostasis and survival, metabolism, and sensitivity to apoptosis.** MAMs are therefore involved in vital cellular functions, but they are dysregulated in several human diseases. Whilst MAM dysfunction is increasingly implicated in the pathogenesis of neurodegenerative diseases, its role in amyotrophic lateral sclerosis (ALS) is poorly understood. However, in ALS both ER and mitochondrial dysfunction are well documented pathophysiological events. Moreover, alterations to lipid metabolism in neurons regulate processes linked to neurodegenerative diseases, and a link between dysfunction of lipid metabolism and ALS has also been proposed. In this review we discuss the structural and functional relevance of MAMs in ALS and how targeting MAM could be therapeutically beneficial in this disorder.

1. Introduction

In neurons, the mitochondria and endoplasmic reticulum (ER) are important for cellular function, and dysfunction to both organelles is implicated in **amyotrophic lateral sclerosis** (ALS) [1]. ALS, one of the motor neuron diseases (MND), is a fatal neurodegenerative disorder affecting both upper motor neurons in the brain and lower motor neurons in the brainstem and spinal cord. The majority of ALS patients die within 2–5 years of diagnosis due to respiratory failure. Familial ALS (fALS) is caused by genetic mutations in 5–10% of cases [2], whereas the remaining instances arise sporadically. The most common mutations are hexanucleotide repeat expansions in the chromosome 9 open reading frame 72 *(C9orf72)* gene, representing 40% of fALS and approximately 7% of sporadic cases [3,4]. Mutations in superoxide dismutase 1 *(SOD1)* [5], the first gene linked to ALS, represent another 20% of fALS cases. *TARDBP*, encoding TAR DNA-binding protein-43 (TDP-43), is mutated in another 4% of fALS cases, but remarkably, TDP-43 is found in a pathological form in almost all ALS cases (97%). In fact, TDP-43 pathology, referring to misfolded, hyperphosphorylated, truncated, mis-localised TDP-43, is the characteristic pathological hallmark of ALS [6,7]. Mutations in Fused in Sarcoma (*FUS*), which has striking functional and structural similarities to TDP-43, cause another 4–5% of fALS cases [8,9]. Among other ALS-causative genes, mutations in the gene encoding vesicle-associated membrane-protein-associated protein B (*VAPB*) are responsible for ALS-8 [10]. VAPB is an ER-resident protein involved in vesicle trafficking, calcium (Ca^{2+}) homeostasis and lipid transport [11].

In ALS, mutant VAPB misfolds and forms aggregates, and reduced VAPB expression is observed in sporadic ALS patients and $SOD1^{G93A}$ mice [12,13]. Moreover, mice expressing mutant $VAPB^{P56S}$ develop cytoplasmic TDP-43 and ubiquitin pathology in motor neurons, implying the existence of a link between mutant VAPB and TDP-43 cytoplasmic localisation [14]. Similar to VAPB, sigma-1 receptor (SigR1) is another transmembrane ER protein associated with ALS, and recessive mutations are present in both adult-onset and juvenile-onset ALS (ALS-16) [15]. In addition to the juvenile ALS-associated E102Q missense mutation, a splice site (c.151 +1 G>T) mutation and two novel homozygous mutations (E138Q and E150K) in SigR1 have been reported to cause autosomal recessive distal hereditary motor neuropathy (dHMN) [15–17]. SigR1 is strongly expressed in motor neurons and it functions in regulating Ca^{2+} transfer from the ER to mitochondria [18,19].

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https://doi.org/10.1016/j.semcdb.2021.02.002
Received 24 November 2020; Received in revised form 4 February 2021; Accepted 5 February 2021
Available online 9 March 2021

Mitochondria-associated ER membranes (MAMs) are a region of the ER, rather than being an independent cellular compartment. MAMs represent detergent resistant lipid rafts, and in mouse liver and mammalian cell lines under resting conditions, their intermembrane distance is 10–30 nm [20]. However, it is important to note that the ER-mitochondrial distance and the percentage of MAMs contacting the ER are not established measures and they are dependent on cell type. Furthermore, under cellular stress, these distances may also decrease [21]. MAMs were first recognised in the early 1950's as electron dense structures that localize to specialized domains between the ER and mitochondria [22–25]. Approximately 12% of the outer mitochondrial membrane (OMM) associates with the ER [26]. The existence of these transient contact sites between ER and mitochondria provides an opportunity to synergize the functions of these two organelles. Not surprisingly therefore, MAMs are thought to play pivotal roles in Ca^{2+} signalling, mitochondrial biogenesis, autophagy, intracellular trafficking, redox homeostasis, energy metabolism and cellular survival [27,28]. Moreover, they are involved in many aspects of lipid metabolism, including synthesis, catabolism and re-acylation [29].

Multiple cellular pathogenic mechanisms have been described in ALS, including protein misfolding, mitochondrial dysfunction, defects in RNA metabolism, the ubiquitin proteasome system (UPS) and autophagy, redox signalling and nucleocytoplasmic transport, and induction of ER stress, glutamate excitotoxicity, DNA damage, oxidative stress, and apoptosis [30]. Increasingly, the contribution of MAMs to human pathology and particularly neurodegenerative diseases such as ALS, is becoming recognised. Moreover, dysfunction to the ER and mitochondria is present early in neurodegeneration in ALS disease models, implying that defects to MAMs are involved in pathophysiology [31–33]. In this review we discuss recent evidence describing dysfunction to the MAMs in ALS and how these defects are involved in pathophysiology.

2. Functions of proteins recruited to the MAM compartment

Both the mitochondria and ER are highly dynamic organelles which undergo continuous, co-ordinated remodelling. Proteins and lipids residing in the OMM and ER membrane interact to promote the formation of MAMs, but these interactions are reversible, and do not involve membrane fusion [34]. Thus, MAMs are a specialised subdomain of the ER which resemble the microsomal cellular fraction in terms of their specific lipid and protein compositions [29]. Based on their localization, MAM proteins are classified into three groups; those that localise (1) exclusively in the MAM, (2) in MAMs but also in other subcellular compartments, and (3) temporarily in the MAM. The cellular redox state and palmitoylation, a process by which cysteine residues on a substrate protein are modified to form a thioester with a palmitoyl group, determine whether a protein localises in the MAM or not [35]. Many MAM proteins have been previously identified in cellular lysates obtained from transgenic and cell culture models, using a range of biochemical and proteomic methods [36–39]. More recently, a novel proteomics method, 'Contact-ID', a proximity-labelling technique based on biotinylation activity of two split-BioID components after proximity-dependent reconstitution, was used to profile live cells. This study identified 115 new MAM-localized proteins that were mostly involved in facilitating lipid homeostasis in the MAMs [40].

The key proteins involved in structural organisation and regulation of the MAM compartment include mitofusin 2 (MNF2), a dynamin related GTPase involved in mitochondria juxtaposition and Ca^{2+} signalling [41], inositol 1, 4, 5-triphosphate receptor (IP3R), the main protagonist regulating Ca^{2+} efflux from the ER into mitochondria, glucose-regulated protein 75 (GRP75), which is essential for efficient Ca^{2+} transfer from ER to mitochondria [42], voltage-dependent anion channel 1 (VDAC1), involved in the maintenance of mitochondrial functions, dynamin-related protein 1 (Drp1), a GTPase which regulates mitochondrial morphology [43], and phosphofurin acidic cluster sorting protein-2 (PACS2), which stabilizes and regulates the interaction of ER and mitochondria [44].

Several protein complexes are implicated in tethering between the ER and mitochondria to form the MAM compartment, the first involving MNF2 [41]. This can involve homologous interaction between two MNF2 subunits to form a homodimeric complex, or by heterologous interactions between MNF2 and its homologue, mitofusin 1 (MNF1) [45]. A second protein complex implicated in ER-mitochondrial tethering involves VAPB interacting with mitochondrial protein tyrosine phosphatase-interacting protein 51 (PTPIP51) [46]. Similarly, VDAC1 of the OMM interacts with ER-localised Ca^{2+} release channel IP3R, through the molecular chaperone GRP75 [42,47]. Finally, the multifunctional sorting protein PACS-2 and ER-localised Bap31 have been linked to the formation of MAMs, but whether they are functional scaffolds themselves, or simply regulators of scaffolding protein function, is unclear [48]. However, depletion of PACS-2 in endothelial cells induces Bap31-dependent mitochondrial fragmentation and dissociation from the ER, which activates apoptosis during atherogenesis, providing evidence for a tethering association between these proteins [49]. The MAM compartment is also enriched in regulators of lipid metabolism, such as cholesterol acyltransferase/sterol O-acyltransferase 1 (ACAT1). ACAT1 is a multimembrane spanning enzyme that converts free cholesterol to cholesteryl esters and thus mediates cholesterol homeostasis. The ER chaperone binding immunoglobulin protein (BiP)/GRP78 forms a complex with SigR1 at the MAM and it regulates Ca^{2+} homeostasis between ER and mitochondria. Members of the protein disulphide isomerase (PDI) family, including PDIA1, PDIA3 and ERp44, function as chaperones and oxidoreductases that mediate disulphide bonding in proteins. They also regulate ER homeostasis and the MAMs. Calnexin, HSPA9 and calreticulin are also chaperones that provide a high capacity Ca^{2+} reservoir at the MAMs [44,50]. Thus, MAMs facilitate cellular metabolism by co-ordinating protein folding, oxidation/reduction reactions, lipid synthesis and Ca^{2+} buffering.

3. Overview of lipid signalling in neurons

Lipids are implicated in a wide range of biological processes. The nervous system in particular contains a high lipid content because lipids act as secondary messengers in cellular signalling, synaptogenesis, neurogenesis, impulse conduction and energy supply through the oxidation of fatty acids [51]. Moreover, lipids are critical for neuronal development and plasticity, and their composition significantly affects synaptic vesicle fusion and lipoprotein receptor mobility [52]. Based on the Lipid Metabolites and Pathways Strategy (LIPID MAPS) consortium [53], lipids are divided into 8 categories; fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids and polyketides (derived from condensation of ketoacyl subunits), sterol lipids and prenol lipids (derived from condensation of isoprene subunits) [54]. The reader is directed to several excellent recent reviews that provide more detailed descriptions of lipid structures and synthesis, and how they function in the context of the central nervous system [52,55–57]. Here in brief we only discuss the lipids enriched in the brain.

The brain is particularly enriched in polyunsaturated fatty acids (PUFAs), which are implicated in neuronal signalling processes that regulate neurogenesis, synaptic vesicular activity, glucose homeostasis, inflammation, mood and cognition [58,59]. Phospholipid signalling, involving phosphatidylinositol, is implicated in inter-neuronal communication and vesicular activity [55]. Sterol lipids are vital to cellular function as they act as secondary messengers in developmental signalling. Cholesterol is a sterol lipid that can be synthesised by humans. Gangliosides are a large family of glycosphingolipids with important roles in membrane protein modulation, cell-cell adhesion, axonal growth, synaptic transmission, neural development and differentiation, and nerve growth factor receptor regulation [60]. While individual lipids can play crucial roles in neuronal lipid signalling, some cellular processes are driven by more complex lipid structures, such as lipid rafts,

which are discussed in detail in Section 5.

4. Regulation of lipids at the MAMs

MAMs are fundamental to cellular function because they co-ordinate the transport of phospholipids, and with the ER, are the only organelles that can *de novo* synthesize phospholipids [61]. In fact, the first functions ascribed to MAMs were lipid synthesis and lipid trafficking between the ER and mitochondria in rat liver [29]. The transport of lipids at the MAMs is thought to be both vesicular and non-vesicular (independent of membrane bound vesicles), and this is vital for lipid synthesis and metabolism. However, it should be noted that many aspects of lipid transport are under debate. In addition, to facilitate non-vesicular lipid transfer from the ER to mitochondria, MAMs are enriched in sphingolipids and cholesterol, which provide robust solidity to these membranes, and they insulate MAMs from the hydrophilicity of the cytosol [62]. MAMs also contain several enzymes that synthesise lipids, including ACAT1, diacylglycerol O-acyltransferase 2 (DGAT2), phosphatidylserine synthases 1 and 2 (PSS1 and PSS2), phosphatidylethanolamine N-methyltransferase 2 (PEMT2), fatty-acid CoA ligase 4 (FACL4/ACS4), fatty acid transport protein 4 (FATP4), and stearoyl-CoA desaturase 1 (SCD1) [62,63]. PEMT2 is considered to be to be a specific marker for MAMs because when it was first identified from rodent liver/primary hepatocytes, it was not present in bulk ER fractions [62,64]. Similarly, FACL4, which is involved in the ligation of fatty acids to coenzyme A (CoA), is also considered to be a specific MAM marker protein [65]. MAMs also contain secretory proteins, including microsomal triacylglycerol transfer protein, which is required for secretion of apolipoprotein B-containing lipoprotein [62]. This suggests that MAMs may be involved in the secretory pathway and they may function in assembling nascent very low-density lipoproteins (VLDL).

Protein complexes located in the MAMs are responsible for biosynthesis of two of the most abundant cellular phospholipids, phosphatidylcholine (PC) and phosphatidylethanolamine (PE) [61]. Moreover, multiple phospholipids and glycosphingolipid-synthesizing enzymes are present on the MAMs, and they support the transfer of lipids between the ER and mitochondria [55]. Indeed, another phospholipid, phosphatidylserine (PS), is synthesized in the ER by the MAM-localised enzymes PSS1 and PSS2. The newly formed PS is transferred to the outer surface of the mitochondrial inner membrane *via* the MAM, where it is decarboxylated into PE by phosphatidylserine decarboxylase. Subsequently, PE returns to the ER, whereby PEMT2 mediates the synthesis of PC [66]. MAMs are also rich in cholesterol, and they consist of enzymes essential for cholesterol biosynthesis [67]. Under cellular stress conditions, the flux of cholesterol changes due to either increased hydrolysis of stored cholesteryl esters or transport of free cholesterol into the mitochondria. Moreover, increased levels of cholesterol within the MAMs is associated with several diseases, including Alzheimer's disease (AD) and cancer [68,69].

Adenosine triphosphatase (ATPase) family member AAA domain containing protein 3 (ATAD3) is enriched at the MAMs. ATAD3 participates in the regulation of steroidogenesis, a process involved in channelling cholesterol between the ER and mitochondria *via* the formation of MAMs [70]. Lipid binding proteins, such as oxysterol-binding protein (OSBP)-related proteins (ORPs), facilitate the exchange of sterols between the ER and mitochondria. This process is aided by phosphatidylinositol 4-phosphate localised at the MAMs, which facilitates cholesterol transport between the ER and mitochondria [71]. ORP5 and ORP8 are two other family members partially targeted to MAMs that interact with PTPIP51. Deletion of these proteins alters membrane dynamics and the morphology of mitochondria, although it is unclear how these proteins control lipid and cholesterol transport [72]. Caveolin, a sterol interacting protein, plays a pivotal role in regulating intracellular transport of cholesterol and MAM organization in hepatic cells [73]. MAMs are also involved in sphingolipid metabolism and thus contain enzymes such as sphingomyelinase [74], which produces ceramide from the hydrolysis of sphingomyelin. Importantly, increased ceramides are associated with induction of apoptosis [75]. The presence of sphingomyelin phosphodiesterase (SMase), ceramide synthase (CerS), and dihydroceramide desaturase (DES) at MAMs also represents a central checkpoint control mechanism to prevent the influx of ceramide, and thus regulate apoptosis [74,76,77].

5. MAM constituents of lipid rafts

The close association of phospholipids, cholesterol and sphingolipids leads to the formation of lipid rafts [78], which are major organizing centres for proteins and essential cellular signalling components [79]. Lipid rafts in the brain are found in both neurons and glia and they have been implicated in neurotransmitter transport, actin remodelling, exocytosis, cell metabolism, neuronal growth and redox signalling [79–81]. High levels of both cholesterol and sphingolipids in lipid rafts render the MAM membranes more rigid. This drives phase separation of sphingolipids from the phospholipid-rich outer membrane, transforming the MAMs into liquid-ordered domains. Moreover, phospholipids in raft-like domains contain longer and more saturated acyl chains compared to non-raft membranes, which increases the thickness of MAMs. This facilitates the recruitment of target proteins into liquid-ordered domains [82]. Interestingly, the presence of enzymes invovled in lipid metabolism within lipid rafts results in the formation of glycosphingolipid-enriched microdomain fractions at the MAMs [83]. In the ER, endoplasmic reticulum lipid raft protein (erlin) 1 and erlin-2 are associated with lipid synthesis and form lipid rafts at the ER [84]. Importantly, mutations in erlin-2 are observed in primary lateral sclerosis (PLS) [85]. SigR1 forms raft-like microdomains and targets lipid droplets to the ER [86,87], and its depletion can destabilize lipid rafts [88]. Lipid rafts in the MAMs also contribute to the formation of autophagy-associated vesicles in human fibroblasts [89]. Alterations in lipid rafts have been detected in the frontal cortex of brains of AD patients, where lower levels of docosahexaenoic acid and oleic acid were identified compared to controls [90]. One previous study demonstrated that instability of raft microdomains appears to be a critical and early event in the development of synucleinopathies in Parkinson's disease (PD). Lipid rafts from the frontal cortex of PD patients display reductions in long-chain polyunsaturated fatty acids compared to controls, suggesting the presence of dysregulated lipid raft signalling and cognitive decline during the development of PD [91]. In contrast, the composition and pathophysiology of the MAMs in ALS has not been well studied but it is now gaining increasing attention [92–94].

6. Evidence of MAM dysfunction in ALS

Mounting evidence now suggests that MAM dysfunction is an important pathological mechanism in ALS, and it has been reported for several ALS-associated proteins. Several proteins mutated in fALS, notably VAPB and SigR1, are present within the MAM compartment, where they are implicated in forming the contacts between ER and mitochondria. The fALS VAPB mutant protein P56S displays increased binding to PTPIP51, which is important for maintaining MAM connections between the ER and mitochondria compared to wildtype VAPB, in HEK293 cells [95]. Thus expression of mutant $VAPB^{P56S}$ leads to reduced ER-mitochondria associations, which perturbs MAM morphology, leading to increased Ca^{2+} release from the ER, consequently augmenting mitochondrial Ca^{2+} uptake in cellular models [95]. Similarly, in another study, overexpression of mutant $VAPB^{P56S}$ in rat cortical neurons perturbed resting cytosolic Ca^{2+} levels, which reduced anterograde transport of the mitochondria along the axons of these neurons [96].

Interestingly, the MAM associations mediated by VAPB-PTPIP51 can be disrupted by expression of both wildtype and mutant TDP-43 or FUS, through activation of glycogen synthase kinase-3β (GSK-3β) in cell lines, which decreases mitochondrial Ca^{2+} levels [97,98]. Overexpression of

wildtype FUS in mice reduces the number of ER–mitochondrial contacts and results in less VAPB–PTPIP51 interactions, leading to neurodegeneration and a ALS-like phenotype, including hind-limb paralysis and reduced survival [97]. Furthermore, tightening ER-mitochondria contacts, either by overexpression of VAPB or PTPIP51, or by the use of a synthetic linker protein that artificially tethers the two organelles together, reduces autophagosome formation in cellular models [99]. In contrast, downregulation of VAPB or PTPIP51 expression using siRNA loosens ER and mitochondrial contacts and induces autophagosome formation in cell culture. Thus, together, these data indicate that the VAPB-PTPIP51 tether, which forms the structural connection between the ER and mitochondria, regulates formation of the autophagosome, and thus autophagy [99].

SigR1 controls the export of cholesterol and galactoceramide, and ER-mitochondrial Ca^{2+} signalling by chaperoning the IP3R receptor, which modulates Ca^{2+} [100]. SigR1 forms a complex with BiP at the MAMs which counteracts ER stress in Chinese hamster ovary (CHO) cells [100]. Upon ER $\mathbf{Ca^{2+}}$ depletion, SigR1 dissociates from BiP, leading to prolonged Ca^{2+} signalling into mitochondria *via* IP3Rs [100]. Importantly, IRE1α is activated by reactive oxygen species (ROS) produced by mitochondria located at the MAMs, and it is stabilized by SigR1 in cells undergoing ER stress [101]. Moreover, knockdown of SigR1 in CHO cells enhances apoptosis by glucose deprivation [100]. SigR1 is also important in maintaining motor function because SigR1 knockdown in mice leads to motor impairment [102]. Interestingly, expression of SigR1 is reduced significantly in human sporadic ALS spinal cords and is abnormally distributed in sporadic and fALS motor neurons [103]. Normally, SigR1 is located in postsynaptic densities associated with cholinergic synapses (C-terminals), whereas in ALS patients it accumulates in enlarged C-terminals and in the ER of motor neurons [103]. Furthermore, knockdown of SigR1 in neuronal cells leads to structural deformities in the ER, ER stress and the formation of ER-derived autophagic vacuoles, suggesting that it alters MAM composition [103]. In motor neurons of SigR1 knockout mice, increases in intracellular Ca^{2+} and ER stress, and reduced ER-mitochondrial contacts were detected [104]. Expression of ALS-associated SigR1 mutation E102Q in cellular models also resulted in ER swelling, widening of the MAMs and induction of both ER and proteotoxic stress [15,105]. In addition, knockout of SigR1 aggravated MAM perturbation in mutant $SOD1^{G85R}$ transgenic mice, indicating that MAMs are perturbed in both SigR1 and SOD1-linked ALS [106]. SigR1 is detected in non-neuronal cells, including oligodendrocytes and Schwann cells, in the rat brain [107,108]. Moreover, SigR1 facilitates the formation of galactosylceramide-enriched lipid rafts and regulates oligodendrocyte differentiation in the rat sciatic nerve [109]. Importantly, non-neuronal cells, such as astrocytes, microglia, and oligodendrocytes, directly contribute to neurodegeneration in ALS by a non-cell autonomous mechanism. However, the role of SigR1 in non-neuronal cells has not been explored in the context of ALS. MAMs have been mostly investigated in whole tissue fractions, hence their role in specific cell types has not been addressed.

Bcl-2 is an important protein present at mitochondrial OMM and MAMs, where it promotes cellular survival by inhibiting pro-apoptotic proteins. Bcl-2 interacts with mutants $SOD1^{G37R}$, $SOD1^{G41D}$, and $SOD1^{G85R}$ *in vitro* and with $SOD1^{G93A}$ *in vivo,* which subsequently disrupts IP3R activity by decreasing Ca^{2+} levels [110–112]. Mutant, but not wildtype SOD1, is found at the MAM in neuronal cells and spinal cords of end-stage mutant $SOD1^{G85R}$ and $SOD1^{G93A}$ mice [106]. SOD1 mutants are thought to gain toxic functions in ALS, implying that aberrant binding of mutant SOD1 to the OMM could prevent the association of mitochondrial proteins with the ER. Moreover, mutants $SOD1^{G93A}$ and $SOD1^{G85R}$ bind to VDAC1, which reduces VDAC1 channel conductance in lysates of rat spinal cords [113]. Miro1, a Rho-GTPase which regulates mitochondrial transport along microtubules by linking mitochondria to kinesin and dynein molecular motors, is also located at MAMs. Moreover, decreased levels of Miro1 were observed in transgenic $SOD1^{G93A}$ mice, and inhibition of axonal transport of mitochondria was detected in HEK293 cells [114]. These studies imply that mutations in SOD1 could affect MAM function in ALS. Furthermore, expression of Miro1 was significantly reduced in spinal cord tissues of ALS patients and transgenic mice expressing $SOD1^{G93A}$ or ALS-TDP-43^{M337V} [115].

7. Lipid dysregulation in MAM in ALS

The studies detailed above describe protein abnormalities at the MAMs in ALS. However, defects to lipids and enzymes involved in lipid metabolism have also been observed in ALS. Modification of the lipid composition of the MAMs also influences apoptosis in disease models. Lower levels of glycosphingolipids were detected in ALS patient spinal cords and inhibition of glycosphingolipid synthesis in $SOD1^{G93A}$ mice aggravated disease progression, thus implicating glycosphingolipids in ALS pathogenesis [116]. Recently, increased levels of ceramides and cholesteryl esters were observed in the spinal cord of $SOD1^{G93A}$ rats [117]. RNA-sequencing and lipidomic profiling demonstrated that altered levels of sphingolipids were present in spinal cords of symptomatic $SOD1^{G86R}$ mice [118], providing further evidence that modifications to cholesterol metabolism are associated with ALS. Interestingly, incubation of arachidonic acid promoted the formation of mutant $SOD1^{A4V}$ aggregates in a dose and time-dependent manner *in vitro,* suggesting that unsaturated fatty acids might promote the formation of an aggregation-prone conformation in mutant SOD1 [119]. However, it should be noted that similar lipid abnormalities are found in other neurodegenerative diseases, implying that lipid dysfunction may be a common pathology associated with neurodegeneration. Increased levels of cholesterol stimulate the production and accumulation of amyloid-β in primary cultures of hippocampal neurons and mixed cortical neurons. Furthermore, specific isoforms of the cholesterol transporter apolipoprotein E are associated with susceptibility in AD patients, suggesting the existence of a link between lipid metabolism (especially cholesterol) and susceptibility to AD [120–122]. Inhibiting the activity of ACAT decreases Aβ production in both neurons and non-neuronal cells, suggesting that cellular cholesterol esters stimulate amyloid-β production in AD [123]. Lipids also modulate α-synuclein oligomerization. Studies using Spin Labels in Electron Spin Resonance (ESR) Spectroscopy and fluorescence spectroscopy revealed that α-synuclein interacts with sphingomyelin and cholesterol-containing small vesicles, which affected lipid packing into these vesicles [124].

Reticulon (RTN) protein 1C is known to facilitate lipid trafficking [126] and reticulons are also implicated in the pathogenesis of ALS [125,126]. Overexpression of RTN-1 C leads to decreased content of lipids and inhibited MAM function in neuronal cells [126]. The $VAPB^{P56S}$ mutation may also dysregulate lipid transfer from ER to mitochondria due to its ability to interact with ER-localised OSBP. Indeed, expression of mutant $VAPB^{P56S}$ prevents localization of OSBP within the ER, and reduces phosphoinositide phosphatidylinositol-4-phosphate (PI4P) balance, significantly retarding neurite extension in NSC-34 cells [127].

7.1. MAM associated redox proteins and their role in ALS

Oxidative stress induces oxidation of lipids and alters lipid metabolism, and it is a commonly described pathophysiological mechanism in ALS. Lipids are major targets of redox dysregulation and oxidative stress results in lipid peroxidation *via* a chain-reaction process whereby ROS attacks PUFAs of cellular membranes, leading to their functional and/or structural impairment. Lipid peroxidation and cholesterol esterification have both been associated with ALS [128,129]. Abnormalities in sphingolipid and cholesterol metabolism have been detected in spinal cord lysates prepared from ALS patients and mutant $SOD1^{G93A}$ mice [128,129]. Inhibition of sphingolipid synthesis prevents the accumulation of ceramides, sphingomyelin and cholesterol esters, and protects motor neuronal apoptosis induced by oxidative stress.

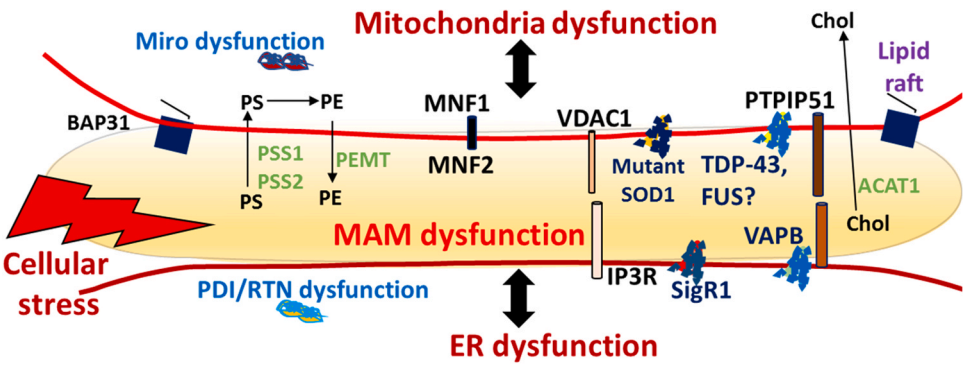

Fig. 1. Hypothetical model illustrating the key MAM proteins and MAM dysfunctions described in ALS. ALS associated proteins, including mutant forms of SigR1, VAPB, SOD1, TDP-43, FUS, and dysfunction in PDI/RTN, induce defects in the MAM compartment, which induces and/or aggravates ER and mitochondrial dysfunction. Moreover, defects in tethering complexes (MNF1, MNF2, PTPIP51, BAP31) and lipid rafts affect the levels of important lipids such as cholesterol (Chol), and ceramides. The important functional MAM enzymes (PSS1, PSS2, PEMT and ACAT1) are shown in green (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Given that lipids are major targets of redox dysregulation, and that oxidative stress is an important pathophysiological mechanism in ALS, it is also important to consider how MAM-localised proteins involved in redox regulation are perturbed in ALS. The ER and mitochondria are both redox-sensitive organelles that produce ROS, and together they control the cellular redox balance [130]. Hence, not suprisingly, accumulation of ROS within these organelles perturbs MAM functions, including ER–mitochondria Ca^{2+}/lipid exchange and oxidative protein folding within the ER. Redox dysregulation inactivates MAM-localized IP3R in cultured endothelial cells, which is essential to maintain Ca^{2+} homeostasis [131]. MAMs are also enriched in chaperones and oxidoreductases including calnexin, TMX1, PDIA1, PDIA3, ERp44 and Ero1α [132,133]. These chaperones bind to ER-localised Ca^{2+} handling proteins and they regulate ER-mitochondrial Ca^{2+} flux and, consequently, modulate mitochondrial metabolism *via* redox-dependent interactions [134]. Moreover, calnexin shuttles between the rough ER and MAMs depending on its palmitoylation status, which is the only redox regulated lipid modification that can be reversibly controlled [135]. When palmitoylated, calnexin facilitates Ca^{2+} signalling, whereas non-palmitoylated calnexin associates with PDIA3 and regulates protein quality control, but not Ca^{2+} regulation [132]. During ER stress, the MAMs become depleted of calnexin, which increases ER-mitochondrial Ca^{2+} flux in HeLa cells [132]. Similarly, the ER-localized thioredoxin--like protein TMX4 is targeted to MAMs upon palmitoylation [136]. Mutation of the palmitoylation sites within TMX4 disrupts palmitoylation and their enrichment at MAMs. Thus, palmitoylation appears to be key for MAM enrichment of ER membrane proteins. Interestingly, Ero1α, which regulates oxidative folding with PDIA1, also regulates Ca^{2+} signalling at the MAMs. However, it becomes depleted under a reducing milieu in cultured cells [138]. Translocation and localization of the Ero1-Lα isoform to the MAMs depends on the oxidoreductase status of the ER. During ER stress, Ero1-Lα oxidizes IP3R1, and hence promotes release of Ca^{2+} from the ER [133]. Furthermore, ERp44, another PDI family member localised at MAMs, binds to IP3R1 and inhibits its activity under reducing conditions in the ER [139]. This then inhibits Ca^{2+} transfer to mitochondria localised within the MAMs [139].

In ALS, the redox activity of PDIA1 is protective against mutant TDP-43 and mutant SOD1 in neuronal cells and zebrafish models [140]. Interestingly, in contrast, in Huntington's models, PDIA1 localises at the MAMs and induces apoptosis in PC12 cells [141]. However, the function of PDI family members in the MAMs has not been specifically defined in ALS. Since ER stress and redox dysfunction are both observed in ALS [142], it could be speculated that these oxidoreductase proteins may localise on the MAMs and induce pathological events. Another thiol regulated protein, P66Shc, regulates redox signalling and apoptosis and it localizes to the mitochondrial side of the MAM membrane. Activation of P66Shc by mutant $SOD1^{G93A}$ and $SOD1^{H80R}$ strongly inhibits activity of the small GTPase Rac1 through a redox-sensitive mechanism, inducing apoptosis in human neuronal cells [143]. Interestingly, a proteomics study demonstrated that C9orf72 is enriched in the mitochondrial fraction of neuronal cells, and C9orf72 also interacts with MAM proteins, including VDAC3 and RTN-4 [137]. Therefore, future studies investigating the role of C9orf72, which is mutated in the majority of fALS cases, is warranted.

7.2. *Therapeutics based on targeting the MAM compartment*

Disruption to MAM function mostly manifests as defective ER–mitochondria associations, which induces ER and/or mitochondria stress and disturbs calcium homeostasis. It is therefore tempting to speculate that MAM dysfunction could be a common starting point for neuronal degeneration [33]. Given that expression of both wildtype and mutant TDP-43 results in loosening of MAM contacts by breaking of the VAPB–PTPIP51 tethers, small molecules that inhibit TDP-43-induced MAM damage may be potential therapeutic targets [98]. Moreover, therapeutics based on targeting the MAMs may be beneficial it they have the potential to restore both ER and mitochondrial function. To this end, an agonist of SigR1 (Pre-084) improved muscle activity, motor performance and extended survival in pre-symptomatic ALS $SOD1^{G93A}$ mice [144]. Furthermore, another SigR1 agonist (SA4503) facilitated cytoplasmic calcium clearance in $SOD1^{G93A}$ motor neuron cultures [145]. Similarly, salubrinal, an ER stress inhibitor, restored calcium homeostasis in SigR1-deficient cultured motor neurons [104]. This suggests that compounds targeting ER stress may also improve MAM function. However, our understanding of the MAMs comes mainly from studies of individual MAM proteins or associated interacting partners. It is harder to probe how the functions of the intact MAMs are perturbed in ALS, and which functions contribute most to pathogenesis. Hence, in therapies targeting the MAMs, it is important to consider the functions of the MAMs as a whole, and how they could be targeted without compromising the other functions of both ER and mitochondria.

8. Conclusion

The ER is not isolated, but rather forms contact sites with many other organelles, including the mitochondria, Golgi, peroxisomes, endosomes, lysosomes and plasma membrane. Among these, the contacts between the ER and mitochondria at MAMs are the most well-characterized organelle contact sites. MAMs act as a hub for Ca^{2+} handling, redox signalling, mitochondrial morphology, lipid synthesis and transport, autophagy, inflammation and apoptosis. The links between alterations of MAMs and ALS are becoming well documented, although the directionality of these associations and their underlying origins remain largely unknown. Therefore, understanding the molecular composition and functions of MAMs, and the mechanisms that control ER-mitochondrial apposition, will be of fundamental importance in ALS (Fig. 1). Therapeutic strategies based on modulating functions of the MAMs may therefore be beneficial in the future.

Acknowledgements

This work was supported by the National Health and Medical Research Council of Australia (NHMRC) Project grants (1006141, 10305133, 1086887, and 1095215). Additionally, support was from the Motor Neurone Disease Research Institute of Australia, Angie Cunningham Laugh to Cure MND Grant and Zo-ee Research Grant, and Grants in Aid, and the FightMND Foundation.

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