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REVIEW

SUBJECT COLLECTION: MITOCHONDRIA

Endoplasmic reticulum–mitochondria signaling in neurons and neurodegenerative diseases

Andrea Markovinic^{1,*}, Jenny Greig^{1,2,*}, Sandra María Martín-Guerrero¹, Shaakir Salam¹ and Sebastien Paillusson^{1,3,‡}

ABSTRACT

Recent advances have revealed common pathological changes in neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis with related frontotemporal dementia (ALS/FTD). Many of these changes can be linked to alterations in endoplasmic reticulum (ER)–mitochondria signaling, including dysregulation of Ca²⁺ signaling, autophagy, lipid metabolism, ATP production, axonal transport, ER stress responses and synaptic dysfunction. ER–mitochondria signaling involves specialized regions of ER, called mitochondria-associated membranes (MAMs). Owing to their role in neurodegenerative processes, MAMs have gained attention as they appear to be associated with all the major neurodegenerative diseases. Furthermore, their specific role within neuronal maintenance is being revealed as mutant genes linked to major neurodegenerative diseases have been associated with damage to these specialized contacts. Several studies have now demonstrated that these specialized contacts regulate neuronal health and synaptic transmission, and that MAMs are damaged in patients with neurodegenerative diseases. This Review will focus on the role of MAMs and ER–mitochondria signaling within neurons and how damage of the ER–mitochondria axis leads to a disruption of vital processes causing eventual neurodegeneration.

KEY WORDS: Endoplasmic reticulum, MAMs, Mitochondria, Tethers, Neurons, Neurodegenerative diseases

Introduction

Mitochondria have a major role in the energy metabolism of eukaryotic cells (McBride et al., 2006). However, the long-held dogma that mitochondria are only the 'powerhouse of the cells' has now been firmly abandoned owing to extensive work showing that mitochondria also play an essential role in several other cellular functions, including regulation of Ca²⁺ homeostasis, apoptosis, cell growth and differentiation, and reactive oxidative species (ROS) production among others (McBride et al., 2006). In order to spatially and temporally orchestrate different cellular mechanisms, mitochondria rely on the signals from other organelles and in particular the endoplasmic reticulum (ER). Indeed, ER and

mitochondria form close contacts through specialized regions of ER called mitochondria-associated membranes (MAMs) (Csordas et al., 2006). MAMs are dynamic structures composed of membrane segments from both the outer mitochondrial membrane (OMM) and the ER, as well various proteins (Box 1) (Csordas et al., 2006). The mechanism by which MAMs are recruited to the mitochondrial surface involve ER–mitochondrial tethering proteins that physically link the organelles (Csordas et al., 2006; Rowland and Voeltz, 2012). Alterations to ER–mitochondria tethering and MAMs have been strongly linked to the pathogenesis of major neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis with related frontotemporal dementia (ALS/FTD) (Lau et al., 2018; Paillusson et al., 2016). Interestingly, several functions that are regulated by ER–mitochondria signaling are disrupted in neurodegenerative diseases, including bioenergetics and mitochondrial ATP production, Ca²⁺ homeostasis, axonal transport, lipid metabolism, inflammation, autophagy, ER stress responses and the unfolded protein response (UPR) (Paillusson et al., 2016). However, it is yet to be elucidated whether disruption of ER–mitochondria signaling is a primary trigger of neurodegeneration and an early step in a cascade of pathogenic mechanisms involved in neuronal death, or a repercussion of different cellular insults that subsequently heighten the process of neurodegeneration.

Neurons in particular are dependent on functional ER–mitochondria signaling, not only due to their high energy demands, but also because ER–mitochondria interactions are involved in axonal transport and neurotransmission (Gomez-Suaga et al., 2019; Hirabayashi et al., 2017; Paillusson et al., 2016). Thus, in this Review, we will focus on the role of ER–mitochondria signaling in neurons and discuss how tethering and regulatory proteins that shape communications between the two organelles contribute to key neuronal functions. Finally, we will describe the evidence for disruption in the ER–mitochondria axis in several neurodegenerative diseases.

The critical role of ER–mitochondria contacts and signaling in neuronal biology

ER–mitochondria contacts and signaling are important since they impact upon so many different cellular functions (Csordas et al., 2018; Paillusson et al., 2016). However, recent evidence has uncovered ER–mitochondria signaling roles specifically within neurons. The use of electron microscopy to investigate ER–mitochondria contacts in brain has revealed that these contacts are extensive within neurons, being present in cell bodies, axons, dendrites and synaptic regions (Hirabayashi et al., 2017; Leal et al., 2018; Wu et al., 2017b).

One of the primary functions of ER–mitochondria signaling is the regulation of intracellular Ca²⁺ homeostasis (Hajnoczky

¹Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 9RX, UK.

²Inserm, Centre de Recherche en Transplantation et Immunologie, UMR 1064, ITUN, 44093, Nantes, France. ³Université de Nantes, Inserm, TENS, The Enteric Nervous System in Gut and Brain Diseases, IMAD, Nantes, 1 rue Gaston Veil, 44035, Nantes, France.

*These authors contributed equally to this work

‡Author for correspondence (sebastien.paillusson@univ-nantes.fr)

Box 1. Type of proteins present at the MAMs

MAMs are specialized ER subdomains, which form physical interaction with the mitochondrial surface in order to orchestrate some of the key cellular functions (Csordas et al., 2006). At the MAMs, ER and mitochondria are closely apposed (10–30 nm), and it has been estimated that 5–20% of the total mitochondrial surface is in close contact with ER membranes (Csordas et al., 2006). Within the MAMs, four major types of proteins can be found based on their role. The first category are tethering proteins (e.g. VAPB, PTPIP51 and MFN2), which mediate physical anchoring between the organelles (Csordas et al., 2006). The second type of proteins present at the MAMs are the regulatory proteins such as SigmaR1. These proteins regulate the interaction between tethers and the activity of other resident proteins at the MAMs (Tsai et al., 2009b). The third type of proteins at these contact sites carry out functions that are related to MAM biology and include IP3R, VDAC and fatty acid-CoA ligase 4 (FACL4; also known as ACSL4) (Csordas et al., 2018; Wieckowski et al., 2009). The fourth type are ER-resident proteins that are enriched in MAMs where they regulate several ER functions, such as calnexin or calbindin (Wieckowski et al., 2009). For comprehensive reviews, see Aoyama-Ishiwatari and Hirabayashi (2021) and Csordas et al. (2018).

et al., 2000). The main pathway for Ca^{2+} transfer from ER stores to mitochondria involves release of Ca^{2+} by inositol 1,4,5-trisphosphate receptors (IP3Rs) and import into mitochondria via the OMM voltage-dependent anion channel (VDAC) proteins (VDAC1–VDAC3) and the inner mitochondrial membrane (IMM) protein mitochondrial Ca^{2+} uniporter (MCU) (Rizzuto et al., 1998) (Fig. 1). Ca^{2+} is required for mitochondrial ATP production because dehydrogenases in the TCA cycle are Ca^{2+} dependent (Rowland and Voeltz, 2012; van Vliet et al., 2014). Ca^{2+} plays a vital role in sparking synaptic transmission as concentrations of presynaptic Ca^{2+} control neurotransmitter release, while changes in dendritic Ca^{2+} levels regulate synaptic activity (Devine and Kittler, 2018; Segal, 2005; Sjostrom et al., 2008). Moreover, release of Ca^{2+} from intracellular stores orchestrates neurogenesis by activating signaling pathways that are involved in proliferation, differentiation and migration (Toth et al., 2016).

Remarkably high concentrations of mitochondria in synaptic terminals were reported over 60 years ago (Palay, 1956), and their presence is now known to be linked to the high levels of ATP required for synaptic activity (Laughlin et al., 1998). In addition, the ER is also present in synaptic regions, where ER–mitochondria contacts are now known to form (Gomez-Suaga et al., 2019; Hirabayashi et al., 2017; Mironov and Symonchuk, 2006). Synaptic activity is also dependent on mitochondrial fission, that is, depletion of the key mitochondrial fission protein dynamin-related protein 1 (Drp1; also known as DNML1) leads to impairment in synaptic transmission and memory functions (Oettinghaus et al., 2016) (Fig. 1). As Drp1 has a potential role in stabilizing the interaction between ER and mitochondria, its loss and subsequent disruption of synaptic transmission could be directly linked to impaired signaling between the two organelles (Oettinghaus et al., 2016; Prudent et al., 2015).

Pathological conditions such as axonal injury has been shown to trigger recruitment of ER and mitochondria to the damaged site (Han et al., 2016; Rao et al., 2016; Zhou et al., 2016). Interestingly, an increase in ER–mitochondria tethering and subsequent Ca^{2+} transfer to mitochondria promotes regrowth of injured axons (Lee et al., 2019) thus pointing to ER–mitochondria signaling as a potential therapeutic target in neurodegenerative diseases (Fig. 1).

Finally, ER–mitochondria signaling is also involved in the regulation of autophagy and mitophagy (selective degradation of damaged mitochondria) (Son et al., 2012). Moreover, a core component of many neurodegenerative diseases is autophagic dysfunction (Hara et al., 2006; Nixon, 2013). However, the role of ER–mitochondria contacts in autophagy is somewhat controversial. Although it has been initially shown that ER–mitochondria contacts are sites for autophagosome formation (Hamasaki et al., 2013), subsequent work has reported that loss of ER–mitochondria contacts stimulates autophagy (Gomez-Suaga et al., 2017; Rimessi et al., 2020; Wu et al., 2018) (Fig. 1), possibly due to the different methods used to induce autophagy.

ER–mitochondria tethering proteins in neurons

Many years after electron microscopy revealed the occurrence of close interactions between ER and mitochondria (Robertson, 1960; Shore and Tata, 1977), the first tether protein complex was discovered in yeast and termed the ER–mitochondria encounter structure (ERMES) (Kornmann and Walter, 2010). PDZD8 is a mammalian homolog of one subunit of the ERMES complex, but its mitochondrial binding partner is unknown (Fig. 1). Although it is not clear how PDZD8 acts as a tether, it has been shown to promote ER–mitochondria contacts and induces Ca^{2+} delivery to mitochondria at the synapse in cortical neurons (Hirabayashi et al., 2017). Several other mammalian proteins have also been identified as ER–mitochondrial tethers.

The interaction between IP3R, VDAC and the glucose-regulated protein 75 (GRP75; also known as HSPA9) was one of the first proposed tethering complexes (Rizzuto et al., 1998) (Fig. 1). This complex has a functional role in directing Ca^{2+} transfer between ER and mitochondria and subsequent ATP production (Bartok et al., 2019; D’Eletto et al., 2018; Rapizzi et al., 2002; Szabadkai et al., 2006a). However, a complete knockout of all three isoforms of IP3R does not modify ER–mitochondria contacts, suggesting that the IP3R–GRP75–VDAC complex associates at contact sites rather than being a bona fide tether (Csordas et al., 2006).

Homotypic and heterotypic interactions between mitochondrial mitofusin 1 (MFN1) and/or mitofusin 2 (MFN2) and ER-located MFN2 have also been proposed as a tethering complex (de Brito and Scorrano, 2008, 2009). Although MFN2 appears to regulate MAM dynamics, its role as genuine tether is still debated, as a loss of MFN2 expression has been reported to both decrease and increase mitochondrial contacts (Cosson et al., 2012; de Brito and Scorrano, 2008; Filadi et al., 2015; Leal et al., 2016; Naon et al., 2016; Wang et al., 2015).

Several studies have suggested that the interaction between the integral ER protein vesicle-associated membrane protein-associated protein B (VAPB) and the OMM component protein tyrosine phosphatase interacting protein 51 (PTPIP51; also known as RMDN3) acts as a major linker between ER and mitochondria (Cieri et al., 2018a; De Vos et al., 2012; Rimessi et al., 2020; Stoica et al., 2014; Yeo et al., 2021) (Fig. 1). More recently, an interaction between VAPB and PTPIP51 was found within neuronal synapses, where it contributes to synaptic activity (Gomez-Suaga et al., 2019). Here, we primarily focus on the three major ER–mitochondria tether complexes mentioned above, and further proteins identified as MAM tethers are listed in Table 1.

Regulators of ER–mitochondria signaling and their links to neuronal functions

ER–mitochondria contacts are now known to change in response to physiological stimuli and are increased by induction of synaptic

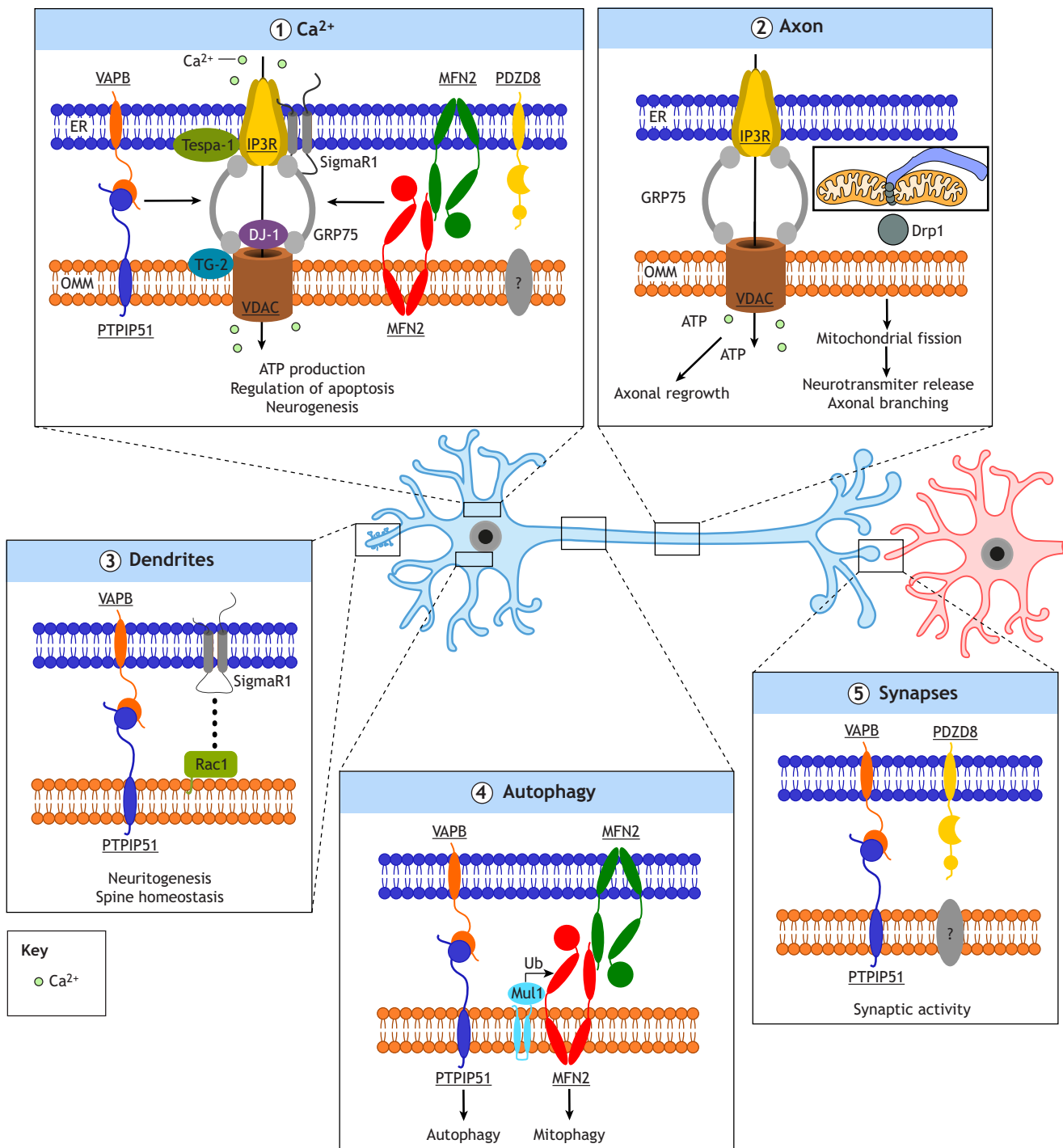


Fig. 1. ER–mitochondria interactions and signaling regulates key neuronal functions. (1) Regulation of Ca²⁺ homeostasis is a key function of ER–mitochondria signaling in neurons. The main route of Ca²⁺ transfer between these organelles is via the IP3R–GRP75–VDAC tether, and is facilitated by Tespa-1, DJ-1 and TG-2, which stabilize the complex by interaction with GRP75. In addition, SigmaR1 binds and chaperones the IP3R to ensure optimal Ca²⁺ signaling through the MAMs. The VAPB–PTPIP51 tether and MFN2 oligomers facilitate Ca²⁺ transfer from ER to mitochondria via IP3R–GRP75–VDAC by bringing the organelles into close contact. Although its mitochondrial binding partner is still not known, PDZD8 also regulates tethering of the organelles and Ca²⁺ transfer in neurons. (2) Under physiological conditions, GRP75 only has a small effect on promoting normal axonal development. Upon axonal injury, loss of GRP75 inhibits regrowth of injured axons, while its overexpression promotes regrowth by ensuring Ca²⁺ transfer from ER to mitochondria and subsequent ATP production. The fission mediator protein Drp1 stabilizes ER–mitochondria interactions and orchestrates mitochondrial division in neurons. Its role in mitochondrial fission is crucial in the regulation of neurotransmitter release and axonal branching. (3) In dendrites, VAPB and PTPIP51 have been shown to regulate the number of dendritic spines, whereas SigmaR1 regulates spines formation through the ER–mitochondria–Rac-GTP pathway. The dotted line indicates an interaction, but no direct tethering. (4) Autophagy in neurons is crucial for the removal of damaged proteins and organelles in order to maintain neurotransmission, synaptic plasticity and neuronal survival. The VAPB–PTPIP51 tethering complex inhibits autophagy by mediating ER–mitochondria Ca²⁺ exchange. In addition, the E3 ubiquitin ligase Mul1 ubiquitylates MFN2 and targets it for degradation, which subsequently increases ER–mitochondria contacts. This, in turn restricts mitochondrial degradation. (5) At synapses, tethering between VAPB and PTPIP51 is necessary for optimal synaptic activity, while ER–mitochondria signaling regulated by PDZD8 promotes postsynaptic Ca²⁺ homeostasis. Tether proteins are shown underlined.

Table 1. List of proteins identified as MAM tethers

Protein name	Location	TM domain	Disease	Binding partners	Expression in neurons	Data independently replicated	References
ATAD3A	IMM/OMM	1 or 2 (if dimer)	HD	WASF3 GRP78	Yes++	Yes	Gilquin et al., 2010; Issop et al., 2015; Zhao et al., 2019
Bap31	ER	1		Fis1	Yes+	No	Iwasawa et al., 2011
EI24	ER	5		VDAC	Yes+	Yes	Yuan et al., 2019; Zheng et al., 2018
Fis1	OMM	1		Bap31	Yes (spinal cord++)	No	Iwasawa et al., 2011
FUNDC1	OMM	3		IP3R2	Yes++	Yes	Wu et al., 2019, 2017a, 2016
GRP75	MAMs	0	AD	IP3R (all isoforms) VDAC (all isoforms)	Yes+	Yes	D'Eletto et al., 2018; Szabadkai et al., 2006a
INF2	ER	1		SPIRE1C	Yes+	No	Korobova et al., 2013; Manor et al., 2015
IP3R1	ER	1	AD	VDAC	Yes++	Yes	Bartok et al., 2019; Csordas et al., 2006; Szabadkai et al., 2006a
IP3R2				GRP75	Yes+		For a review see, Csordas et al., 2018
IP3R3				FUNDC1	Yes+		
MIGA2	OMM	2		VAPB	Yes+	No	Freyre et al., 2019
MFN2	ER/OMM	2	CMT	MFN1/MNF2	Yes+	Debated	Cosson et al., 2012; de Brito and Scorrano, 2008; Filadi et al., 2015; Leal et al., 2016; Wang et al., 2015
MOSPD2	ER	1		PTPIP51	Yes++	No	Di Mattia et al., 2018
ORP5	ER	1		PTPIP51	Yes+	No	Galmes et al., 2016
ORP8							
PDZD8	ER	1		unknown	Yes+	No	Hirabayashi et al., 2017
PTPIP51	OMM	1	AD/PD/ ALS/FTD	VAPB ORP5/8 MOSPD2	Yes++ (hippocampus+++)	Yes	Cieri et al., 2018a; De Vos et al., 2012; Di Mattia et al., 2018; Fecher et al., 2019; Galmes et al., 2016; Qiao et al., 2017
SPIRE1C	OMM	2		INF2	Yes+++	Yes	Manor et al., 2015
SYNJ2BP	OMM	1		RRBP1	Yes+	No	Hung et al., 2017
REEP1	ER/OMM	2		REEP1 (homodimer)	Yes++	No	Lim et al., 2015
RRBP1	ER	1		SYNJ2BP	Yes+	No	Hung et al., 2017
VAPB	ER	1	AD/PD/ ALS/FTD	PTPIP51	Yes+++	Yes	Cieri et al., 2018a; De Vos et al., 2012
VDAC1	OMM	1	AD	IP3R	Yes++	Yes	De Stefani et al., 2012; Szabadkai et al., 2006a, 2006b
VDAC2				GRP75			
VDAC3							

+++ , high expression; ++ , medium expression; + , low expression. Protein expression levels in neurons were annotated according to the Human Protein Atlas database (www.proteinatlas.org/).

activity (Gomez-Suaga et al., 2019). The mechanism underlying these changes is not fully understood yet, but a number of proteins are known to regulate ER–mitochondria contacts, either to promote or disrupt them. These can act in close vicinity to the contacts such as Sigma-1 receptor (SigmaR1) or can operate more distally by initiating a cascade of signaling events that eventually results in a modulation of contacts, as is the case for ALS-linked proteins TAR DNA-binding protein 43 (TDP-43; also known as TARDBP) and fused in sarcoma (FUS) (Hayashi and Su, 2007; Stoica et al., 2014, 2016).

SigmaR1 is predominantly localized at MAMs where it acts as an IP3R chaperone to facilitate the transfer of Ca²⁺ from ER to mitochondria and support the synthesis of ATP (Hayashi and Su, 2007; Mavlyutov et al., 2010). Moreover, SigmaR1 regulates dendritic spine formation in hippocampal neurons via activation of Rac1, a small Rho GTPase involved in regulation of neuronal development (Tsai et al., 2009a; Watabe-Uchida et al., 2006) (Fig. 1). Ca²⁺ transfer from ER to mitochondria at MAMs is also facilitated by Tespa-1, transglutaminase type 2 (TG-2; also known as TGM2) and the deglycase DJ-1 (also known as PARK7), which

physically interact with GRP75 to stabilize the IP3R–GRP75–VDAC complex (D'Eletto et al., 2018; Liu et al., 2019; Matsuzaki et al., 2013) (Fig. 1). In addition, the E3 ubiquitin ligase MITOL (also known as March5 and MARCHF5) promotes ER–mitochondria interaction by stimulating MFN2 oligomerization; accordingly, its loss in neurons leads to a disruption of ER–mitochondria contacts, oxidative stress and neuroinflammation (Nagashima et al., 2019; Sugiura et al., 2013).

Maintenance of mitochondrial function is of key importance for neurons, not only due to their high energetic requirements, but also as a protection against the generation of neurotoxic ROS (Angelova and Abramov, 2018). The mitochondrial E3 ubiquitin ligase Mulf1 protects mitochondrial morphology, restrains mitophagy and promotes ER–mitochondria coupling in neurons by targeting MFN2 for degradation, thus acting as a positive regulator of ER–mitochondria contacts (Puri et al., 2019) (Fig. 1). In addition, Mulf1 promotes SUMOylation of Drp1 to stabilize its oligomers on the mitochondrial membrane, which subsequently promotes ER–mitochondria interactions and regulates the release of pro-apoptotic factor cytochrome *c* (Prudent et al., 2015). Moreover, Drp1 plays a

crucial role in mitochondrial fission, which is particularly important in neurons for the maintenance of normal synaptic transmission and terminal branching during the final step of axon development (Lewis et al., 2018; Oettinghaus et al., 2016) (Fig. 1). Loss of the OMM proteins Miro1 and Miro2 leads to disruption of ER–mitochondria interactions and mitochondrial cristae morphology, although the precise mechanism is still unclear (Modi et al., 2019). Moreover, Miro1 forms a complex with disrupted-in-schizophrenia 1 (DISC1) to promote anterograde mitochondrial transport in neuronal axons, which is known to have a crucial role in development of neurons and neurotransmission (Ogawa et al., 2013). DISC1 also orchestrates Ca^{2+} transfer from ER to mitochondria and disrupts ER–mitochondria contacts by binding to IP3R, thus precluding binding of its ligand, while its loss results in Ca^{2+} overload in mitochondria and the generation of oxidative stress in neurons (Park et al., 2017).

The serine/threonine-protein kinase Akt1 localizes to MAMs and has been linked to neurodegeneration (Betz et al., 2013; Giorgi et al., 2010). Akt1 has been shown to play a role in the maintenance of ER–mitochondria contacts, which may be linked to its ability to phosphorylate IP3Rs (Betz et al., 2013). The full list of regulators of ER–mitochondria interactions and their functions are listed in Table 2.

Given that either mutations or disruption in function of the abovementioned tethers and regulators have been reported in several neurodegenerative diseases, in the following sections we will focus on highlighting the role of ER–mitochondria signaling in common neurodegenerative diseases.

ER–mitochondria signaling and AD

AD is the most common form of dementia, currently affecting more than 55 million people worldwide (World Alzheimer Report 2021; <https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf>). Its key pathologic hallmarks are plaques composed of extracellular amyloid β ($A\beta$) peptides and intracellular neurofibrillary tangles formed of highly phosphorylated aggregates of the Tau protein, a microtubule-associated protein found at greater levels in the brains of AD patients compared to controls (Goedert and Spillantini, 2006; Khatoon et al., 1994; Masters et al., 2015). $A\beta$ is generated by cleavage of amyloid precursor protein (APP) by two proteases known as β -secretase and γ -secretase. Presenilin 1 (PS1) and presenilin 2 (PS2) (also known as PSEN1 and PSEN2, respectively) are active subunits of the γ -secretase complex, and mutations in genes encoding for presenilin proteins and APP cause some familial forms of AD (Goedert and Spillantini, 2006; Schellenberg and Montine, 2012).

Several lines of evidence suggest that MAMs and ER–mitochondria signaling may play a key role in the pathogenesis of AD. First, the levels of proteins tethering or associating with MAMs, including VAPB, PTPIP51, IP3R1, MFN1, MFN2, phosphofurin acidic cluster sorting protein 2 (PACS-2) and SigmaR1, were found to be either increased or decreased in post-mortem AD brain tissue (Hedskog et al., 2013; Lau et al., 2018; Leal et al., 2020; Sepulveda-Falla et al., 2014). Moreover, disruption to ER–mitochondria contacts, including damage to VAPB–PTPIP51 tethers (Lau et al., 2020), is present in human post-mortem AD tissue, even at early disease stages (Hedskog et al., 2013; Lau et al., 2018; Leal et al., 2018; Sepulveda-Falla et al., 2014). Second, MAMs are a platform for major proteins linked to AD pathogenesis and are enriched in both PS1 and PS2, whereas acyl-CoA:cholesterol acyltransferase, an enzyme proposed to be necessary for $A\beta$ production, is predominantly located at

MAMs (Area-Gomez et al., 2009; Puglielli et al., 2001; Rusinol et al., 1994). Third, upon cleavage of full-length APP by β -secretase, the intermediate fragment, called C99, is transported to MAMs and processed by γ -secretase to form two peptides, amyloid precursor protein intracellular domain (AICD) and $A\beta$ (Pera et al., 2017). Thus, MAMs are sites of $A\beta$ production (Area-Gomez et al., 2009; Schreiner et al., 2015). Finally, the E4 allele of apolipoprotein E (ApoE4), a major genetic risk factor for AD, promotes ER–mitochondria communication and MAM function (Tambini et al., 2015) (Fig. 2).

Most of the evidence for impaired ER–mitochondria signaling in AD arises from cellular and transgenic mouse models. However, these studies present conflicting data; whereas some studies have reported that PS2 is important for modulating ER–mitochondria signaling (Rossi et al., 2021; Zampese et al., 2011) and that PS1 is dispensable in this process (Zampese et al., 2011), others have shown that PS1 does affect ER–mitochondria interactions (Area-Gomez et al., 2012; Sepulveda-Falla et al., 2014). Interestingly, AD-linked PS2 mutants diminish mitochondrial Ca^{2+} uptake while increasing ER–mitochondria contact sites (Area-Gomez et al., 2012; Filadi et al., 2016; Kipanyula et al., 2012; Zampese et al., 2011), suggesting increased ER–mitochondria interaction as a cell-intrinsic compensatory mechanism to boost transfer of Ca^{2+} from ER to mitochondria. The effect of $A\beta$ and APP on ER–mitochondria interactions has also resulted in conflicting data, with some studies showing increased contacts (Del Prete et al., 2017; Hedskog et al., 2013; Leal et al., 2020), whereas others have reported decreased contacts (Martino Adami et al., 2019). In addition, expression of disease-associated phosphorylated (Perreault et al., 2009) and truncated Tau (Cieri et al., 2018b) increases the number of ER–mitochondria contact sites. Similar to what is seen for PS2 mutants, truncated Tau has been reported to decrease the basal levels of ER Ca^{2+} . Thus, the subsequent increase in ER–mitochondria contact sites is perhaps acting to restore mitochondrial Ca^{2+} homeostasis (Cieri et al., 2018b) (Fig. 2).

It has also been investigated how loss of ER–mitochondria tethering and diminished MAM function affect AD pathogenesis. Indeed, two studies show that loss of MFN2 decreases γ -secretase activity and lowers $A\beta$ production; however, loss of MFN2 has been suggested to both reduce (Area-Gomez et al., 2012) and increase (Leal et al., 2016) ER–mitochondria contacts. From a clinical point of view, modifying ER–mitochondria interactions could be a potential treatment for AD, as a *Drosophila* model of AD demonstrated that the expression of a synthetic linker, which increases contacts between ER and mitochondria, successfully enhanced locomotion of the flies and expands their lifespan (Garrido-Maraver et al., 2019). However, even though damage to ER–mitochondria contacts is established in AD, data are still conflicting, partly due to the heterogeneity of experimental models and methods used (see Box 2).

ER–mitochondria signaling in PD

PD is the second most frequent neurodegenerative disease, clinically characterized by a motor tetrad, resulting from a loss of dopaminergic neurons in the *substantia nigra pars compacta* (Damier et al., 1999). This loss of dopaminergic neurons is mostly associated with the presence of proteinaceous aggregates, named Lewy bodies, in the surviving neurons; these are mostly composed of phosphorylated and aggregated α -synuclein (Kalia and Lang, 2015).

α -Synuclein is a key protein in PD physiopathology and point mutations and duplications in its encoding gene, *SNCA*, are responsible for familial forms of PD (Srinivasan et al., 2021). Four

Table 2. Overview of regulators of ER–mitochondria signaling

Regulator	Promotor or disruptor	Cellular localization	Mechanism of action	Cellular processes it promotes or disrupts	Expression in neurons	References
Akt	Promotor	MAMs	Interacts with mTORC2, phosphorylates IP3R to regulate Ca ²⁺ release from ER	Ca ²⁺ transfer, apoptosis	Yes+++	Betz et al., 2013; Szado et al., 2008
α -synuclein	Disruptor (when overexpressed or mutant)	MAMs	Binds to VAPB and prevents its binding to PTPIP51	Ca ²⁺ transfer, ATP production	Yes+++	Paillusson et al., 2017
CAV1	Promotor	ER, MAMs	n/a	Transfer of cholesterol	Yes+	Sala-Vila et al., 2016
DISC1	Disruptor	MAMs	Binds directly to IP3R and prevents binding of its ligand	Ca ²⁺ transfer	Yes++	Park et al., 2017
DJ-1	Promotor	MAMs, cytoplasm, mitochondria and nucleus	Interacts with IP3R3-Grp75-VDAC1	Ca ²⁺ transfer	Yes++	Liu et al., 2019
Drp1	Promotor	Cytosol	Stabilises ER-mitochondria contacts when SUMOylated by Mul1	Cell survival, mitochondrial fission	Yes+++	Prudent et al., 2015
FUS	Disruptor	Nucleus	Activates GSK-3 β	Ca ²⁺ transfer, ATP production	Yes+++	Stoica et al., 2016
GSK3 β	Disruptor	Cytoplasm	Brakes VAPB-PTPIP51 interactions	Ca ²⁺ transfer, ATP production	Yes+++	Stoica et al., 2014, 2016
IRBIT/AHCYL1	Promotor	ER	Binds to IP3R	Ca ²⁺ transfer, apoptosis	Yes+(neuropil)	Bonneau et al., 2016
Miro-1/2	Promotor	OMM	n/a	Mitophagy, mitochondrial transport	Miro 1 Yes+++ Miro 2 Yes+	Berenguer-Escuder et al., 2020; Modi et al., 2019
MITOL/MARCH5	Promotor	OMM	Promotes MFN2 oligomerization	Ca ²⁺ transfer, phospholipid transfer	Yes+++	Nagashima et al., 2019; Sugiura et al., 2013
mTORC2 complex: mTOR mLST8 Protor Rictor SIN1 Mul1	Promotor	Cytoplasm, ER, MAMs	Promotes assembly of the IP3R–GRP75–VDAC complex	Ca ²⁺ transfer	Yes++ Yes++ Yes+ Yes+++	Betz et al., 2013
PACS-2	Promotor	ER, mitochondria	Stabilises BAP31	Ca ²⁺ transfer, apoptosis	Yes++	Simmen et al., 2005
PP2A	Promotor	MAMs	Dephosphorylates Akt, upregulates SigmaR1 expression	Ca ²⁺ transfer	Yes++	Betz et al., 2013; Placido et al., 2017
SigmaR1	Promotor	MAMs	Stabilises IP3R and protects it from ERAD	Ca ²⁺ transfer and ATP production; cell survival	Yes++	Hayashi and Su, 2007
Tespa1	Promotor	MAMs	Binds to GRP75	Ca ²⁺ transfer	Yes++	Matsuzaki et al., 2013
TDP-43	Disruptor	Nucleus	Activates GSK-3 β	Ca ²⁺ transfer, ATP production	Yes+++	Stoica et al., 2014
TG-2	Promotor	Cytoplasm, mitochondria	Regulates interaction between GRP75 and IP3R3	Ca ²⁺ transfer	Yes+	D'Eletto et al., 2018
Trichoplein/mitostatin	Disruptor	MAMs	Regulates contacts vis MFN2	Apoptosis	Yes++	Cerqua et al., 2010

+++, high expression; ++, medium expression; +, low expression. Protein expression levels in neurons were annotated according to the Human Protein Atlas database (www.proteinatlas.org/).

groups have reported that modulating alpha synuclein expression affects ER-mitochondria signaling and its associated functions, such as Ca²⁺ homeostasis (Cali et al., 2012; Paillusson et al., 2017), phospholipid synthesis (Guardia-Laguarta et al., 2014), autophagy (Cali et al., 2012), and ATP production (Faustini et al., 2019; Paillusson et al., 2017). However, there is no clear consensus on the

effects of α -synuclein on ER–mitochondria contacts. Initially, overexpression of α -synuclein was found to increase MAM contacts and mitochondrial Ca²⁺ in HeLa cells (Cali et al., 2012, 2019). However, we and another group have subsequently shown that overexpression of α -synuclein results in a decrease in ER–mitochondria interactions and associated functions, and it appears

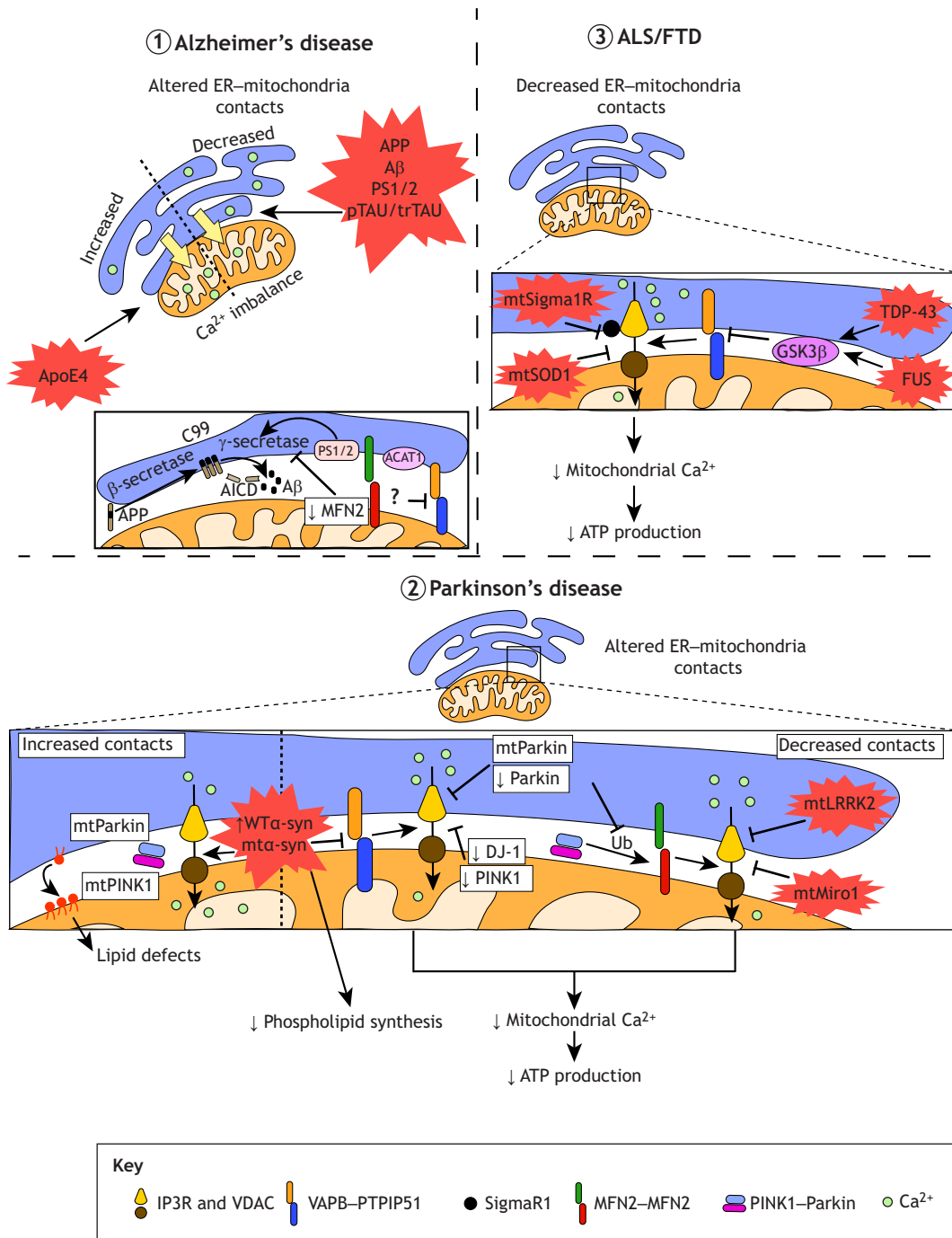


Fig. 2. See next page for legend.

that the familial α -synuclein mutations A53T and A30P have a similar effect (Guardia-Laguarta et al., 2014; Paillusson et al., 2017). One possible reason for this discrepancy might be the relative levels of α -synuclein expressed in the respective models, as well as the methods used (Box 2). Another key point is that α -synuclein is found within the MAM compartment (Guardia-Laguarta et al., 2014; Paillusson et al., 2017), probably due to its high affinity for lipid rafts (Fortin et al., 2004). We have shown that α -synuclein localized at MAMs binds to VAPB and prevents its interaction with PTPIP51, therefore decreasing ER-mitochondria contacts, and demonstrating that α -synuclein can directly break ER-mitochondria contacts (Paillusson et al., 2017) (Fig. 2).

Loss-of-function mutations in PTEN-induced putative kinase 1 (PINK1) and Parkin (an E3 ubiquitin ligase; symbol PRKN), two proteins involved in mitophagy, are responsible for familial forms of PD (Berenguer-Escuder et al., 2019; Cali et al., 2013; Celardo et al., 2016; Gautier et al., 2016; Gelmetti et al., 2017; Parrado-Fernandez et al., 2018). Notably, they both localize to the MAM compartment (Gelmetti et al., 2017; Van Laar et al., 2015), suggesting a role in the regulation of ER-mitochondria signaling (Fig. 2). It has also been found that PINK1- and Parkin-mediated phospho-ubiquitylation of MFN2 complexes promotes their degradation, and subsequent loss of ER-mitochondria contacts, as well as increased mitophagy (Gautier et al., 2016; Gegg et al., 2010; McLelland et al., 2018).

Fig. 2. ER–mitochondria signaling is affected in AD, PD and ALS/FTD.

Schematic illustration of possible mechanisms that disrupt ER–mitochondria signaling in AD, PD and ALS/FTD. The main disruptors of ER–mitochondria signaling are indicated in the red star shapes. (1) In AD, both an increase and a decrease in ER–mitochondria contacts have been reported. Major proteins linked to AD pathogenesis, including A β , APP, presenilin 1 and 2 (PS1/2) and phosphorylated Tau (pTau) or truncated Tau (trTau), alter ER–mitochondria contacts. ApoE4, a major genetic risk factor for AD, increases ER–mitochondria contacts. In addition, PS1, PS2 and acyl-CoA:cholesterol acyltransferase (ACAT1) have been found at MAMs. MAMs are also the production site for A β , as the intermediate fragment C99, a product of APP cleavage, is transported to MAMs where it is processed into AICD and A β . Interactions between the tethers VAPB and PTPIP51 are disrupted in AD, although the precise mechanism is still elusive. Loss of MFN2 decreases γ -secretase activity and lowers A β production. (2) In PD, a different set of proteins linked to PD pathogenesis alters ER–mitochondria contacts. Wild-type (WT) and mutant forms of α -synuclein (m α -syn), which localize to MAMs, have been shown to decrease ER–mitochondria contacts by reducing the interaction between the VAPB and PTPIP51 tethers, subsequently decreasing mitochondrial Ca $^{2+}$ transfer, ATP production and phospholipid synthesis. Furthermore, overexpression of either wild-type or m α -syn increases ER–mitochondria contacts, leading to a subsequent increase in mitochondrial Ca $^{2+}$. Parkin and PINK1 are located at regions of ER–mitochondria contacts; expression of mutant forms of PINK1 and/or Parkin increases the interactions between the organelles, boosts Ca $^{2+}$ uptake by mitochondria and causes lipid defects by depleting phosphatidylserine from the ER (illustrated to the left of the dotted line). However, loss-of-function of PINK1 and Parkin has an opposite effect and results in decreased contacts between the ER and mitochondria, followed by reduced Ca $^{2+}$ mitochondrial uptake (illustrated to the right of the dotted line). Ablation of DJ-1 expression has the same effect. Moreover, PINK1–Parkin ubiquitylates MFN2 to promote the ER–mitochondria interactions. Accordingly, loss of Parkin impedes this ubiquitylation, decreases the contacts between the organelles and disrupts Ca $^{2+}$ homeostasis. Associations between ER and mitochondria are also disrupted by mutant LRRK2 (mtLRRK2) and mutant Miro1 (mtMiro1). (3) In ALS/FTD, VAPB and SigmaR1 mutations are responsible for familial forms of the disease. TDP-43 and FUS (either wild-type or mutant overexpression) activate GSK3 β , which disrupts the VAPB–PTPIP51 interaction, decreases ER–mitochondria contacts and Ca $^{2+}$ delivery to the mitochondria. Mutant SOD1 (mtSOD1) accumulates at MAMs and dysregulates Ca $^{2+}$ transfer. SigmaR1 binds to IP3R–VDAC complex and facilitates Ca $^{2+}$ transfer to the mitochondria; mutations in this receptor promote the dissociation of ER from the mitochondria, followed by disruption in Ca $^{2+}$ transfer and ATP production.

Conversely, several groups have reported that decreased Parkin or PINK1 expression leads to a loss of ER–mitochondria contacts that is associated with dysregulation of Ca $^{2+}$ homeostasis (Fig. 2) (Basso et al., 2018; Cali et al., 2013; Parrado-Fernandez et al., 2018), suggesting a loss of ER–mitochondria contact in PD. Mechanistically, ubiquitylation of MFN2 on lysine 416 by Parkin has been shown to be a pre-requisite for promotion of ER–mitochondria interaction (Basso et al., 2018). However, some studies showed the opposite; in primary fibroblasts from PD patients and *Drosophila* models expressing loss-of-function mutations of either PINK1 or Parkin have an increase in ER–mitochondria contacts (Celardo et al., 2016; Valadas et al., 2018) that is mediated through the activation of the PKR-like ER kinase (PERK; also known as EIF2AK3), one of the key UPR signal activator proteins (Celardo et al., 2016). This increase in contacts was associated with an excessive phosphatidylserine transfer in the MAMs, which is responsible for sleep disorder in flies, a premotor symptom also found in PD (Valadas et al., 2018). Therefore, although it is evident that PINK1 and Parkin have an important role in ER–mitochondria signaling, their contribution is not fully understood.

The deglycase DJ-1 is small protein that scavenges ROS, and has been strongly associated with PD (Repici and Giorgini, 2019). Loss-of-function mutations or deletion of *PARK7*, the gene encoding DJ-1,

Box 2. Methods to quantify ER–mitochondria associations

Physiological contacts between ER and mitochondria are defined as involving distances of ~10–30 nm (Csordas et al., 2006; Rowland and Voeltz, 2012). Therefore, measuring such a short distance is challenging and explains in part the conflicting results that can be found across the literature. Up to now, electronic microscopy (EM) remains the gold standard to assess these contacts. Unfortunately, EM is slow and cannot fully elucidate the dynamics of ER–mitochondria contacts. The need for a quicker approach and turnaround has led to the development of new methods with their own advantages and flaws. Among these, confocal light microscopy typically analyses the overlap between two stained MAM tethers, using Manders' or Pearson's coefficient (Bravo et al., 2011; Cali et al., 2012) to assess the quantity of interaction. However, given the low resolution of confocal microscopy (300 nm), it is now being replaced by super-resolution microscopy techniques, such as STORM (Paillusson et al., 2017) or STED (Filadi et al., 2018). For a dynamic quantification of ER–mitochondria contacts, cleverly designed molecular probes are available that can be transfected into cells or animals and allow live microscopy and high-throughput assays. Proximity ligation assay (PLA) is another method that has also been proven efficient and offers an adequate resolution (Lau et al., 2020; Stoica et al., 2016). These methods for assessing ER–mitochondria contacts have been extensively discussed and reviewed elsewhere (Giamogante et al., 2020; Wilson and Metzakopian, 2021).

are responsible for early onset forms of PD (Repici and Giorgini, 2019). Although DJ-1 is a cytoplasmic protein, it is also found at ER–mitochondria contact sites, where it promotes contacts (Ottolini et al., 2013; Parrado-Fernandez et al., 2018) (Fig. 2). Moreover, DJ-1 has recently been described to interact with and stabilize the IP3R–GRP75–VDAC complex, therefore increasing ER–mitochondria tethering and facilitating Ca $^{2+}$ exchange between the two organelles to sustain mitochondria needs in Ca $^{2+}$ (Liu et al., 2019); this suggests a positive effect on ER–mitochondria contacts (Fig. 2).

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are the most common cause of familial PD and found in 2% of late-onset sporadic cases (Ferreira and Massano, 2017). Recently, *LRRK2* knockout has been shown to decrease ER–mitochondria contacts in mouse embryonic fibroblasts (Toyofuku et al., 2020). This loss of contact is associated with a decrease in mitochondrial Ca $^{2+}$ uptake and oxidative phosphorylation. Interestingly, the *LRRK2* G2019S mutation, which is characterized by a constitutively active kinase domain, decreases ER–mitochondria contacts (Fig. 2), whereas the artificial kinase-dead *LRRK2* D1994A mutation increases these contacts, suggesting that the *LRRK2* kinase domain can regulate ER–mitochondria associations (Toyofuku et al., 2020). This work also reported that, similar to the action of Parkin or PINK1, *LRRK2* negatively regulates PERK activity through the activation of E3 ubiquitin ligases, such as MARCH5, Mul1 or Parkin itself (Toyofuku et al., 2020), highlighting a potential common pathophysiological mechanism in PD.

The small Rho GTPase Miro1, which is involved in mitochondrial transport, has also recently been implicated in PD pathology. Four loss-of-function mutations in *RHOT1*, the gene encoding Miro1, have been recently found in PD patients (Berenguer-Escuder et al., 2019; Grossmann et al., 2019; Saeed, 2018), and fibroblasts from these patients exhibit a loss of ER–mitochondria contacts associated with a decrease in energetic metabolism and increase in LC3-dependent autophagy (Berenguer-Escuder et al., 2019, 2020; Grossmann et al., 2019; Modi et al., 2019) (Fig. 2). Interestingly, overexpression of PINK1 and Parkin promotes Miro1 degradation in rat neurons (Wang et al., 2011),

whereas loss-of-function mutations in PINK1 lead to increased levels of mitochondrial Ca^{2+} in flies through Miro activation (Lee et al., 2018), therefore providing further support for their role in reducing ER-mitochondria associations (Fig. 2).

ER-mitochondria signaling in ALS/FTD

ALS and FTD are two related and incurable neurodegenerative diseases, and their features can include pathological protein inclusions rich in TDP-43, FUS, superoxide dismutase-1 (SOD1) and dipeptide repeat proteins derived from the *C9ORF72* gene in affected neurons (Arai et al., 2009; Ash et al., 2013; Deng et al., 2010; Mori et al., 2013; Neumann et al., 2006). Mitochondrial dysfunction is a common feature of ALS, and targeting mitochondrial dysfunction, in particular early in the disease process, is a potential therapeutic target, as demonstrated by increased survival in animal models of ALS (Mehta et al., 2019). Disruptions to mitochondrial function and Ca^{2+} regulation have been linked to mutations in the major causative genes of ALS, including *TARDBP*, *FUS*, *SOD1* and the *C9ORF72* repeat expansion, despite these not encoding mitochondrial or ER proteins (Smith et al., 2019). Mutations in genes encoding the MAM proteins VAPB and SigmaR1 are also known to cause ALS (Al-Saif et al., 2011; Nishimura et al., 2004).

Induced pluripotent stem cell (iPSC)-derived motor neurons containing the *C9ORF72* hexanucleotide repeat expansion exhibit a reduced mitochondrial membrane potential, increased ER stress and reduced levels of Bcl-2, an anti-apoptotic protein that modulates cellular Ca^{2+} signaling (Dafinca et al., 2016). Levels of GRP78 (also known as BiP), which is associated with the ER stress response, are also increased, and swollen mitochondria were observed (Dafinca et al., 2016). In these cells, Ca^{2+} homeostasis is also disrupted, with a greater Ca^{2+} release on depolarisation, delayed recovery following glutamate stimulation and reduced levels of calbindin, a cytosolic Ca^{2+} buffering protein, resulting in reduced clearance of excess Ca^{2+} (Dafinca et al., 2020). Furthermore, similar to the phenotype of *TARDBP*-mutant iPSC-derived motor neurons, Ca^{2+} permeable subunits of the glutamatergic receptors AMPA and NMDA are upregulated and mitochondrial Ca^{2+} buffering is inhibited, suggesting that glutamate cytotoxicity, a pathological feature of ALS in motor neurons (Van Den Bosch et al., 2006), is aggravated by impaired mitochondrial Ca^{2+} uptake (Dafinca et al., 2020). *In vivo*, mitochondrial abnormalities are induced by expression of poly-GR, one of the dipeptide repeat protein inclusions that are a pathological feature of *C9ORF72*-ALS. In a mouse overexpression model, poly-GR binds to mitochondrial ATP synthase protein ATP5A1 (also known as ATP5F1A) (Choi et al., 2019); this, in turn, increases its ubiquitylation and subsequent degradation, consistent with the reduced ATP5A1 protein levels seen in patient brains (Choi et al., 2019). These mitochondrial defects in the presence of poly-GR were observed before any other cellular defects became evident, supporting the notion that mitochondrial defects are an early pathogenic event in *C9ORF72*-ALS (Choi et al., 2019).

In both cell models and spinal cords of transgenic mice that overexpress TDP-43 (either the wild-type or a form with ALS-linked mutations, such as M337V), the interaction between the ER-mitochondrial tethers VAPB and PTPIP51 are disrupted. This is due to the modulation of GSK3 β activity by TDP-43, which then disrupts the VAPB-PTPIP51 interaction (Stoica et al., 2014) (Fig. 2). The same is true of models with overexpression of wild-type or ALS-linked mutants of FUS. Indeed, overexpression of aggregation-prone FUS results in decreased VAPB-PTPIP51

interactions, reduced mitochondrial Ca^{2+} uptake and reduced ATP production (Stoica et al., 2016).

Mutant SOD1 accumulates at the MAMs specifically in neurons, possibly due to aberrant binding of the mutant protein to the mitochondrial membrane, where it inhibits ER-mitochondria tethering, notably before the onset of any symptoms in mutant SOD1^{G93A} mice (Watabe-Uchida et al., 2006). Mutant SOD1 also results in reduced ATP production, dysregulation of intracellular Ca^{2+} and a loss of MAM proteins, including SigmaR1, IP3R3 and calreticulin, demonstrating a disruption of MAM function and structure (Watanabe et al., 2016).

The MAM-specific factor SigmaR1 is highly expressed in spinal motor neurons and has been shown to have an important role in ALS, as mutations cause ALS, ALS/FTD and juvenile ALS (ALS16) (Al-Saif et al., 2011; Luty et al., 2010; Ullah et al., 2015). *SigmaR1* mutations cause ALS owing to the inability of the mutant protein to bind to IP3R3s, which induces a dissociation of the ER from mitochondria, resulting in disrupted Ca^{2+} homeostasis and reduced ATP synthesis (Watanabe et al., 2016). The colocalization of SigmaR1 with calreticulin is also reduced and mutant forms mislocalize away from the MAMs (Gregianin et al., 2016). Furthermore, loss of SigmaR1 results in reduction of MAM proteins involved in regulation of Ca^{2+} homeostasis, such as IP3R3 (Bernard-Marissal et al., 2015; Watanabe et al., 2016). SigmaR1 function at MAMs has also been shown to be important in ALS with *SOD1* mutation G85R. SigmaR1 knockout in *SOD1*^{G85R} mice accelerated the disease onset, although SigmaR1 deficiency without the *SOD1* mutation caused only a modest motor phenotype (Watanabe et al., 2016). Mutant SOD1 accumulation and SigmaR1 deficiency combined results in a disruption of the MAMs and mitochondrial dysfunction (Watanabe et al., 2016). Furthermore, SigmaR1 activation in *SOD1*-mutant transgenic mice can prevent the disruption of ER-mitochondrial contacts and restore Ca^{2+} homeostasis (Hyrskyluoto et al., 2013; Ono et al., 2014; Watanabe et al., 2016). This further illustrates the importance of MAMs in ALS and the potential of targeting them to delay disease onset, even in the presence of a known ALS mutation.

Mutations in *VAPB* can also cause ALS, with clinical outcomes ranging from severe ALS with rapid progression, autosomal-dominant ALS8, or late onset spinal muscular atrophy in affected individuals (Borgese et al., 2021; Nishimura et al., 2004). Mutant VAPB forms inclusions in the ER, resulting in alterations to ER structure, which have been suggested to underlie motor neuron pathogenesis in ALS (Fasana et al., 2010; Kuijpers et al., 2013), and the VAPB P56S mutation in particular disrupts axonal mitochondrial transport due to an alteration of Ca^{2+} homeostasis (Morotz et al., 2012). VAPB aggregates in the ER have also been observed in sporadic ALS patients even in the absence of any *VAPB* mutations and without changes in its gene expression (Cadoni et al., 2020).

It is clear that mitochondrial dysfunction and disruption of Ca^{2+} homeostasis are common and important features in ALS pathology, pointing to MAMs as a potential therapeutic target, especially as MAM defects appear to occur early in disease progression. Moreover, in sporadic ALS, therapeutically targeting mitochondrial function may be particularly valuable as it appears to be a common feature to ALS even when a causative mutation has not been identified.

ER-mitochondria signaling in Huntington's disease

Huntington's disease (HD) is a genetic autosomal dominant neurodegenerative disorder caused by the abnormal expansion of CAG repeats in the huntingtin (*Htt*) gene (Wanker, 2000). Such

an expansion generates a polyglutamine (polyQ) stretch at the N-terminus of the Htt protein, resulting in its misfolding and aggregation in the cortical and striatal regions (Finkbeiner, 2011; Gutekunst et al., 1999). Additionally, pathogenesis of HD is also accompanied by mitochondrial abnormalities, such as mitochondrial fragmentation, decreased ATP production, loss of mitochondrial membrane potential and disruption of Ca²⁺ signaling (Lim et al., 2008; Milakovic et al., 2006; Naia et al., 2016; Panov et al., 2002; Rockabrand et al., 2007).

Mitochondrial Ca²⁺ overload, which leads to an opening of permeability transition pores (PTPs) and subsequent release of pro-apoptotic factor, was initially linked to HD (Bezprozvanny and Hayden, 2004; Choo et al., 2004; Panov et al., 2002). Moreover, polyQ-expanded Htt proteins were found to interact with IP3R, resulting in its increased activation in response to IP3 and subsequent excessive Ca²⁺ transfer to mitochondria (Bezprozvanny and Hayden, 2004). Moreover, mitochondrial Ca²⁺ overload has been suggested to result from increased TG-2 expression, which has been detected in the cortex and striatum of HD patients (Min and Chung, 2018). Although many groups have demonstrated changes in Ca²⁺ levels in HD, only one study thus far has directly linked alterations in ER–mitochondria contacts with HD (Cherubini et al., 2020). Here, primary striatal neurons obtained from R6/1 mice, a standardized HD mouse model, showed Drp1-mediated reduction in ER–mitochondria contacts, characterized by a reduced interaction between IP3R3 and VDAC, and a subsequent decrease in transfer of Ca²⁺ from ER stores to mitochondria (Cherubini et al., 2020). Although the exact role of ER–mitochondria interactions in HD is not fully clear, it is evident that Ca²⁺ delivery to the mitochondria plays an important role in disease pathogenesis.

ER–mitochondria signaling in Charcot–Marie–Tooth disease

Charcot–Marie–Tooth (CMT) disease is a motor and sensory peripheral neuropathy characterized by demyelination (damage to the myelin sheath) and/or loss of axonal integrity (Baets et al., 2014). CMT is a hereditary disease and among the causative genes, mutations in *MFN2* have been linked to an axonal form of the disease called CMT2 subtype A (Feely et al., 2011; Zuchner et al., 2004). Indeed, several studies have reported that CMT2A-linked mutations in *MFN2* disrupt ER–mitochondria contacts (Basso et al., 2018; Bernard-Marissal et al., 2019; Larrea et al., 2019). Accordingly, *in vitro* studies have shown that the different CMT-causing mutations in *MFN2* failed to restore damaged ER–mitochondria contacts in *Mfn2*^{−/−} MEFs (Basso et al., 2018; de Brito and Scorrano, 2008). Moreover, silencing of ganglioside-induced differentiation associated protein 1 (GDAP1), whose loss-of-function mutations have also been linked to CMT, causes a decrease in ER–mitochondria contacts and disruption to Ca²⁺ homeostasis in *in vitro* and *in vivo* models (Barneo-Munoz et al., 2015; Gonzalez-Sanchez et al., 2017; Pla-Martin et al., 2013). These findings were recently reproduced as motor neurons derived from *GDAP1*^{−/−} mice showed a reduction in the number of ER–mitochondria contacts, reduced ATP production and disruption of mitochondrial axonal transport (Civera-Tregon et al., 2021). Finally, the gene encoding for IP3R3 was recently identified as a CMT-causing gene, and patient fibroblasts showed disrupted Ca²⁺ homeostasis (Ronkko et al., 2020). These findings further support the importance of ER–mitochondria signaling in the etiology of CMT disease.

Concluding remarks and future perspectives

Accumulating evidence shows that defects in ER–mitochondria signaling are a common feature of almost all neurodegenerative

disorders. Interestingly, proteins linked to familial forms of neurodegenerative disorders, such as α -synuclein or TDP-43, appear to be direct or indirect strong disruptors of MAM dynamics. It is now clear that MAMs are crucial for neuronal functions, and although their complexity is not yet fully understood, recent discoveries have identified key factors involved in MAM structure, regulation and functions. In this regard, the role of the VAPB–PTPIP51 interaction as bona fide MAM tethers is strongly suggested by independent findings. In contrast, the role of MFN2, originally considered as an ER–mitochondria tether, still remains unclear, and it might instead have a role in regulating MAMs. Conversely, SigmaR1 has been described to positively modulate MAM activity such as Ca²⁺ exchange through IP3R activation (Hayashi and Su, 2007), and its activation was demonstrated to mitigate the cellular defects seen in some neurodegenerative diseases such as ALS (Lee et al., 2020; Mancuso et al., 2012), suggesting that modulating ER–mitochondria signaling could be beneficial in neurodegenerative disorders. Nevertheless, future efforts should be directed towards providing further insights into the biological functions of MAMs, especially in terms of their structural and dynamic regulation, as well as identifying new pharmacological or genetic approaches to modulate MAM functions. However, conflicting results in studies of MAM dynamics highlight the need to develop new and appropriate methods for their study (Box 2), but they might also shed light on the different mechanisms that overall damage neuronal functions. Given the role of MAMs in neurodegenerative disorders, promoting MAM function is a promising approach to alleviate patient symptoms or slow down the progression of the disease. In this regard, developing new drug-screening assays is crucial in order to be able to identify candidates, for instance SigmaR1 agonists, that can be safely used in patients.

Competing interests

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