Review

α-Synuclein Interactions in Mitochondria-ER Contacts: A Possible Role in Parkinson's Disease

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Abstract

Endoplasmic reticulum-mitochondria contact sites regulate various biological processes, such as mitochondrial dynamics, calcium homeostasis, autophagy and lipid metabolism. Notably, dysfunctions in these contact sites are closely related to neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis. However, details about the role of endoplasmic reticulum-mitochondria contact sites in neurodegenerative diseases remain unknown. In Parkinson's disease, interactions between α-synuclein in the contact sites and components of tether complexes that connect organelles can lead to various dysfunctions, especially with regards to calcium homeostasis. This review will summarize the main tether complexes present in endoplasmic reticulum-mitochondria contact sites, and their roles in calcium homeostasis and trafficking. We will discuss the impact of α-synuclein accumulation, its interaction with tethering complex components and the implications in Parkinson's disease pathology.

Keywords

mitochondria-ER contact sites, α-synuclein, Parkinson's disease, calcium, mitochondria, endoplasmic reticulum

Introduction

The mitochondria and endoplasmic reticulum (ER) are cellular organelles with pivotal roles in regulating many cellular functions. For example, the ER regulates protein synthesis, transport and folding, and lipid and steroid synthesis (Schwarz and Blower, 2016). On the other hand, the mitochondria are the powerhouse of cells responsible for processing the energetic metabolism, synthesizing adenosine triphosphate (ATP) and regulating cell death signals (Galluzzi et al., 2012). Additionally, the ER and mitochondria are the major cellular organelles associated with calcium (Ca^{2+}) physiology and homeostasis, playing a central role in Ca^{2+} release, buffering and storage (Orrenius et al., 2003; Rossi et al., 2019; Vallese et al., 2020).

The proximity and physical interactions between mitochondria and ER facilitate signaling processes and the continuous exchange of signals between these cellular compartments. Previous studies have shown that even though the outer mitochondrial membrane (OMM) and the ER membrane do not touch each other, they are closely positioned within 10 to 30 nm and form specific microdomains termed mitochondria-ER contacts (MERCs) (Csordás et al., 2006; Wu et al., 2018; Xu et al., 2020).

MERCs are dynamic contact sites between the ER and OMM which can occupy 5–20% of the mitochondrial network surface associated with the ER membrane (Gao et al., 2020; Rizzuto et al., 1998). Consequently, MERCs play a crucial role in Ca^{2+} homeostasis and lipid metabolism and transport, as well as many other cellular processes – e.g., mitochondrial dynamics, apoptosis, and autophagy/mitophagy (Barazzuol et al., 2021). In fact, the Ca^{2+} flux from ER play a central role in mitochondrial physiology regulating several mitochondrial processes, including ATP synthesis and mitochondrial Ca^{2+}-sensitive dehydrogenases in the Krebs cycle (oxoglutarate- and isocitrate-dehydrogenases) and glycolysis (pyruvate-dehydrogenase) (Wilson and Metzakopian, 2021).

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One of the first functions proposed to MERCs was lipid synthesis and transport (Vance, 1990). Lipid synthesis takes place in ER, but requires a cooperation of mitochondrial enzymes, rendering MERCs a favorable region to lipid formation (Barazzuol et al., 2021). Several enzymes involved in lipids biosynthesis are present in MERCs in both mitochondrial and ER sides. Phosphatidylserine synthase-1 (PSS1) and phosphatidylserine synthase-2 (PSS2) are located in ER membrane and metabolize phosphatidylserine, which is then carried to mitochondria to be converted into phosphatidylethanolamine by the action of phosphatidylserine decarboxylase-1 and phosphatidylserine decarboxylase-2 (Barazzuol et al., 2021). Additionally, fatty acid CoA ligase 4 (FACL4) is involved in triacylglycerol synthesis and is considered a MERC marker protein (Lewin et al., 2001). Increasing evidence connects MERCs to macroautophagy (hereafter called autophagy), a catabolic process activated in response to nutrient deprivation or dysfunctional cellular components destined to degradation. Autophagy is characterized by the formation of a double-membrane structure called autophagosome that engulfs and isolates the target substrate, followed by its fusion with lysosome and degradation by lysosomal hydrolases (Mizushima and Komatsu, 2011). Studies suggest that autophagosome biogenesis is initiated in MERCs and regulated by autophagy-related proteins (Atg), such as Atg5 and Atg14L, which can be located in MERCs under starvation (Hamasaki et al., 2013). Additionally, mitophagy, a selective process of degradation of dysfunctional mitochondria, is associated with MERCs, given that PTEN-induced putative kinase 1 (PINK1), parkin and Beclin1 were found in this region after CCCP-induced mitochondrial depolarization (Barazzuol et al., 2020; Gelmetti et al., 2017). Thus, PINK1 and parkin are well-characterized proteins involved in the mitophagy machinery (Narendra et al., 2008; Narendra et al., 2010; Youle and Narendra, 2011). Indeed, evidence has implicated MERC disruption in several pathologies, such as cancer (Kerkhofs et al., 2018; Marchi et al., 2014) and neurodegenerative diseases [e.g., Parkinson's Disease (PD), Alzheimer Disease (AD) and amyotrophic lateral sclerosis] (Xu et al., 2020).

Mitochondria plays an important role in the pathophysiology of PD, as several works demonstrated mitochondrial dysfunctions associated with this pathology. Early evidence was first presented by Schapira et al. (1989), who observed the impairment of mitochondrial respiratory chain complexes in *post mortem* tissues from PD patients. Many studies demonstrated numerous other mitochondrial dysfunctions associated with MERCs in PD, such as deficiency in mitochondria degradation, ATP synthesis and Ca^{2+} homeostasis, and mitochondrial fragmentation (reviewed by Borsche et al., 2021). The description of genetic mutations in PARK genes (which will be soon discussed), such as α-synuclein (α-syn) and DJ-1, revealed that mutated PARK proteins resulted in loss of MERC physiology and stability (Erustes et al., 2021; Guardia-Laguarta et al., 2014; Liu et al., 2019; Paillusson et al., 2017). Nonetheless, novel studies are required on MERC functions and dysfunction mediated by PARK proteins, as well as how this domain can participate in PD physiopathology.

Considering the aforementioned framework, we will briefly discuss the aspects of MERC structure, Ca^{2+} homeostasis and the link to PD pathology.

MERC Tethering Complexes

As previously mentioned, ER and mitochondrial membranes are adjacent in MERCs, but effective contact between membranes does not occur. Likewise, van Vliet & Agostinis (2018) highlight that MERCs should not be considered a static structure that connects ER and mitochondria, but as a flexible and adaptable region capable of adjusting contact sites according to the cell necessities. In this regard, a core of tethering complexes regulates the crosstalk and communication between organelles mediating MERC function. These protein bridges are formed by proteins and channels located in the OMM and ER membrane (Figure 1).

Components related to the mitochondrial dynamic machinery are resident in MERCs and also can interact with ER proteins. Mitofusin 1 and mitofusin 2 (Mfn1/2) have an important role in mitochondrial fusion, because they mediate fusion of OMM; while optic atrophy 1 (Opa1) mediates the fusion of the inner mitochondrial membrane (IMM) (Dorn, 2020; Filadi et al., 2018). Additionally to its function on mitochondrial dynamics, Mfn acts as a tether in MERCs. Mfn2 located in the ER membrane forms a complex with Mfn1/2 in the OMM forming homo- or heterodimer complexes (de Brito and Scorrano, 2008; Detmer and Chan, 2007). The ablation of Mfn2 in fibroblasts and HeLa cells causes a reduction in ER-mitochondria interaction and decreases Ca^{2+} traffic between these organelles (Naon et al., 2016). Conversely, other authors report that the loss of Mfn2 increases contact site formation and increases Ca^{2+} transfer from the ER to the mitochondria (Filadi et al., 2016; Leal et al., 2016). Thus, while Mfn2 influences MERC function, the exact role of the Mfn2-Mfn2/1 tether complex requires further investigation. Another tether complex identified in ER-mitochondria contact sites contains fission protein 1 homolog (Fis1) in the OMM. Fis1 participates in mitochondrial fission recruiting dynamin-related protein 1 (DRP1) (Stojanovski et al., 2004). In fact, mitochondrial fission is associated with MERCs, as ER tubules initiate the constriction of mitochondria to determine the division site (Tilokani et al., 2018), followed by the recruitment of cytosolic DRP1 by adaptors proteins (Fis1, Mitochondrial Fission Factor [Mff], mitochondrial dynamics proteins 49 and 51 [MiD49/51]) to OMM and its oligomerization around the fission site (Ji et al., 2017; Tilokani et al., 2018). Finally, Dynamin2 (Dnm2) is recruited to the constriction ring and finalizes the fission process (Lee et al., 2016). Moreover, mitochondrial Fis1 interacts with the ER-resident B-cell receptor-associated protein 31 (Bap31) during apoptosis, recruiting and activating procaspase-8

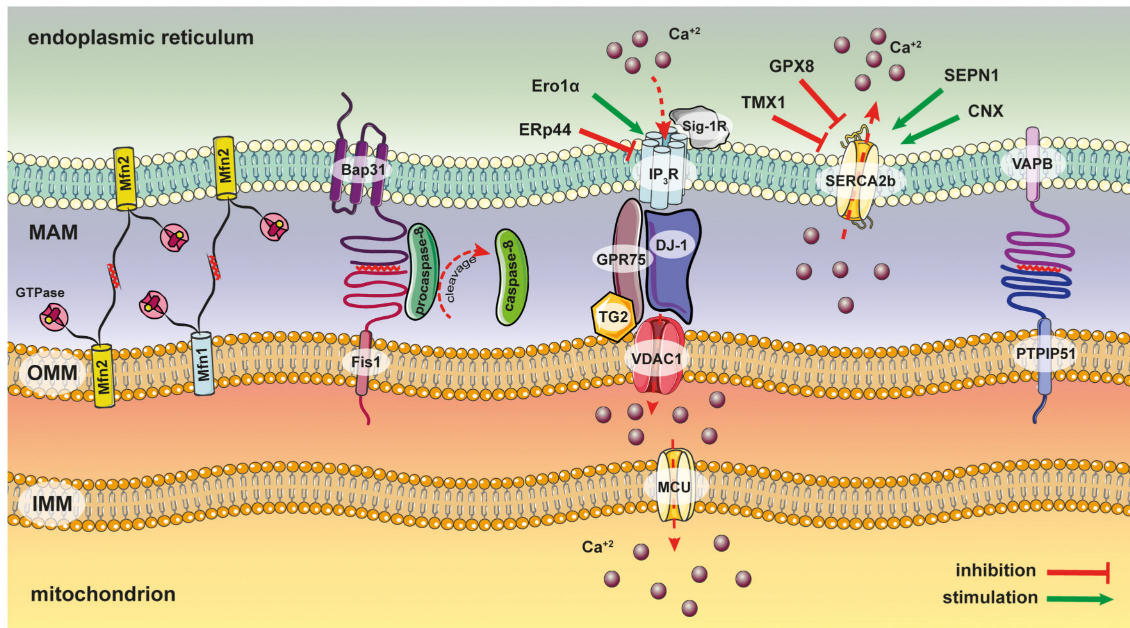

Figure 1. Molecular composition and tethering complexes in MERCs. ER and mitochondria communicate by proteins and channels resident in both ER membrane or the OMM. Mfn2 located in ER membrane interacts with Mfn1/2 in the OMM, forming a homo- or heterodimer complex. The ER resident-protein Bap31 interacts with Fis1 located in OMM during apoptosis, recruiting and activating procaspase 8. The association of VAPB and PTPIP51 facilitates the Ca^{2+} traffic from ER to mitochondria. The IP_3R in ER and VDAC1 in OMM form a complex with two other regulatory proteins, GRP75 and DJ-1, to control the Ca^{2+} transfer from ER to mitochondria. Once in the intermembrane space, Ca^{2+} is transported by MCU to the mitochondrial matrix. Regulatory proteins, such as Sig-1R, inserted in ER membrane, bind to IP_3R stabilizing and enhancing Ca^{2+}; and the TG2 interacts with GRP75 and regulates Ca^{2+} flux and MERCs. IP_3R can be regulated in a redox-sensitive manner by ER-resident proteins, such as Ero1α and ERp44, inducing or inhibiting Ca^{2+} release from IP_3R. SERCA2b is a pump partially located in MERCs that acts transporting Ca^{2+} from cytosol to the ER lumen, and similarly to IP_3R can be regulated by ER chaperones in a redox-sensitive manner. SEPN1 and CNX enhances the SERCA2b activity, increasing the Ca^{2+} levels in ER and reducing its flux to mitochondria. On the other hand, SERCA2b activity is inhibited by TMX1, an ER redox-sensitive reductase, increasing ER-mitochondria contact sites and the Ca^{2+} flux; and by GPX8, which inhibits SERCA2b function and affect the ER- Ca^{2+} storage. The illustration was produced using smart servier medical art vectors for publications and presentations licensed under the Creative Commons 3.0 (CC BY 3.0).

and transferring the apoptotic signal from the mitochondria to the ER. Subsequent caspase-8 activation results in Ca^{2+} release from ER and consequent accumulation in mitochondria (Chandra et al., 2004; Iwasawa et al., 2011), triggering and amplifying the apoptotic signal and activating the mitochondrial machinery to release pro-apoptotic factors.

Another well-established tethering complex in MERCs is formed by the association of the vesicle-associated membrane protein B (VAPB) located in ER and the protein tyrosine phosphatase-interacting protein-51 (PTPIP51) in the OMM (Stoica et al., 2014). VAPB is an integral ER membrane protein, with an N-terminal major sperm protein domain, a central coiled-coil region and a C-terminal transmembrane domain, with roles in membrane trafficking, lipid transfer and metabolism, unfolded protein response and autophagy (Xu et al., 2020). PTPI51 was described as a protein that regulates cellular differentiation, proliferation and apoptosis (Brobeil et al., 2017). Recent findings reported the function of PTPI51 as a phospholipid carrier in MERCs (Yeo et al., 2021). As demonstrated by Stoica et al. (2014), the association of VAPB-PTPI51 in MERCs increases the formation of contact sites and facilitates Ca^{2+} traffic from the ER to the mitochondria. The authors observed the opposite effect when silencing VAPB or PTPI51, resulting in reduction of MERCs and impairment of Ca^{2+} transfer between these organelles, highlighting the role of VAPB-PTPI51 tethering complex in MERC structure and function. Moreover, the VAPB-PTPI51 complex can also regulate autophagy response, and this regulation involves ER-mitochondria Ca^{2+} exchange (Gomez-Suaga et al., 2017).

Previous work has shown that Ca^{2+} flux in MERCs is mediated by the interaction between inositol 1,4,5-triphosphate receptor (IP_3R), an ER Ca^{2+} channel, and the voltage-dependent anion channel 1 (VDAC1) in the OMM (Morciano et al., 2018). Additional to its role in Ca^{2+} signaling, IP_3R also plays a role in the maintenance of MERCs, because IP_3R-deficient cells have reduced ER-mitochondria contact regions (Bartok et al., 2019). This interaction is regulated by the glucose-related protein 75 (GRP75), which increases the juxtaposition of organelles and potentiates Ca^{2+} transfer between the ER and mitochondria (Lv et al., 2018; Szabadkai et al., 2006). After Ca^{2+} levels

increase in the intermembrane space, the mitochondrial calcium uniporter (MCU) transports this ion to the mitochondrial matrix (Xu et al., 2020). The knockdown of GRP75 attenuates Ca^{2+} transfer in MERCs and disrupts mitochondrial homeostasis (Yang et al., 2019).

DJ-1 is a multifunctional protein encoded by the *PARK7* gene, involved in many processes, including apoptosis and pro-survival signaling, autophagy, inflammatory response, and protective role against oxidative stress (Mencke et al., 2021). Mutations in the *PARK7* and loss-of-function of DJ-1 are associated with early onset autosomal recessive PD (Mencke et al., 2021; Zhang et al., 2020). More recently, DJ-1 was described as an IP_3R-GRP75-VDAC1 complex regulator, interacting with its components and modulating its functions (Basso et al., 2020; Liu et al., 2019). Indeed, Liu et al. (2019) demonstrated that DJ-1 ablation impairs the juxtaposition of the ER-mitochondria membranes, disrupts IP_3R-GRP75-VDAC1 interactions, and alters MERC Ca^{2+} homeostasis. The mechanism involved in the integrity loss of IP_3R-GRP75-VDAC1 complex after DJ-1 ablation is still unknown. DJ-1 ablation leads to accumulation and aggregation of IP_3R3 (inositol 1,4,5-triphosphate receptor, type 3) channel at MERCs, which affects the stability of tethering structure and reduces the Ca^{2+} traffic (Liu et al., 2019). On the other hand, DJ-1 overexpression promotes the reestablishment of ER-mitochondria contact sites, which was also impaired after p53 overexpression (Ottolini et al., 2013).

Additionally, regulatory proteins have been shown to interact with the tether complexes assisting in their functions. Transglutaminase-2 (TG2) is a multifunctional enzyme involved in many physiological functions, including cell growth and differentiation, cell death, inflammation, fibrosis, among others regulatory activities, and also might play an essential role in mitochondrial homeostasis, autophagy and mitophagy (Rossin et al., 2015; Tatsukawa and Hitomi, 2021). D'Eletto et al. (2018) demonstrated that TG2 may interact with GRP75 in MERCs, based on the finding that TG2-knockout cells demonstrated a reduction of contact sites and an increase in the distance between ER and mitochondria, resulting in the reduction of Ca^{2+} flux. Another protein with a physiological role in MERCs is the sigma-1 receptor (Sig-1R). Sig-1R can be found in MERCs, where it might act remodeling the cholesterol-enriched microdomains and the structure and composition of lipids in ER-mitochondria contact sites (Zhemkov et al., 2021). Additionally, sig-1R can regulate Ca^{2+} transfer from ER to mitochondria, acting as a molecular chaperone promoting the stabilization of IP_3R and leading to prolonged Ca^{2+} release in MERCs (Hayashi and Su, 2007).

Ca^{2+} Homeostasis in MERCs

ER and mitochondria are the main cellular organelles responsible for Ca^{2+} release and buffering, thus maintaining the cellular Ca^{2+} homeostasis. Therefore, it is not surprising that MERCs play a key role in the crosstalk and homeostasis of Ca^{2+} signaling (Hayashi et al., 2009). Low cytosolic Ca^{2+} concentrations are achieved by pumping the ion into intracellular stores, such as ER and mitochondria. The uptake of Ca^{2+} is mediated by the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA), and its release is induced by inositol 1,4,5-triphosphate (IP_3), a second messenger that functionally interacs with IP_3R or ryanodine (RyR) receptors (Rizzuto et al., 2009). IP_3R occurs in three different isoforms, $IP_3R1/2/3$, with different functions and regulation mechanisms (Bartok et al., 2019). Many studies report IP_3R3 as a marker of MERCs and the main channel related to Ca^{2+} transfer from ER to mitochondria (Mendes et al., 2005), however other studies demonstrate that both isoforms 1 and 2 are located in the ER-mitochondria contact sites (Szabadkai et al., 2006; Wu et al., 2017). Bartok et al. (2019) demonstrate that IP_3R2 is more effective in the release of Ca^{2+} in MERCs, followed by IP_3R3, promoting a large Ca^{2+} efflux from ER to mitochondria. The same authors still mentioned that IP_3R1 is more effective promoting the Ca^{2+} flux through the plasma membrane. After the Ca^{2+} flux through IP_3R, it is captured by VDAC1 in the OMM and transported to the intermembrane space, where it is taken into the mitochondria matrix by MCU (Belosludtsev et al., 2019; Xu et al., 2020).

Furthermore, two important components regulate and participate in the Ca^{2+} transfer from the ER to the mitochondria: the mitochondrial chaperone GRP75 and the DJ-1 protein. Both of them physically interact with IP_3R and VDAC1, forming a tether complex between the ER and the mitochondria, stabilizing the complex and facilitating Ca^{2+} transfer. The downregulation of GRP75 abrogates the functional interaction between these receptors, altering the normal transfer of Ca^{2+} to the mitochondria (Szabadkai et al., 2006). On the other hand, mouse primary neurons overexpressing GRP75 displayed an increase in MERCs, resulting in the elevation of Ca^{2+} traffic from ER to mitochondria and enhanced ATP synthesis (Lee et al., 2019). Additionally, DJ-1 ablation reduces MERCs, disrupting IP_3R-GRP75-VDAC1 interactions and influences Ca^{2+} homeostasis (Liu et al., 2019).

Sig-1R is another notable protein that participates in MERC-mediated Ca^{2+} movement. This Ca^{2+}-sensitive chaperone is inserted in the ER membrane complexed with binding immunoglobulin protein (Bip) or glucose-related regulated protein 78 (GRP78). In Ca^{2+} depleted ER, Sig-1R dissociates from Bip and binds to IP_3R, stabilizing the receptor and enhancing Ca^{2+} flux into the mitochondria (Fujimoto and Hayashi, 2011; Ryskamp et al., 2019).

Ca^{2+} exchange from the ER to the mitochondria is crucial for maintaining mitochondrial function because Ca^{2+} transferred from the ER regulates ATP production in the mitochondria by activating several Ca^{2+}-dependent mitochondrial dehydrogenases involved in the Krebs cycle. For example, pyruvate-, α-ketoglutarate- and isocitrate-

dehydrogenases represent the rate-limiting Krebs cycle steps associated with electron supply into the respiratory chain and generation of proton gradient across the inner membrane (Gellerich et al., 2010). Importantly, as a cofactor of mitochondrial dehydrogenases, Ca^{2+} uptake adjusts cellular metabolism during the production of nicotinamide adenine dinucleotide (NADH), and increased Ca^{2+} concentrations in the matrix stimulate various components of the tricarboxylic acid cycle (TCA), resulting in increased energy production (Giorgi et al., 2018).

Many of metabolic functions of ER and mitochondria are also linked to oxidative metabolism, as these organelles are the major sources of reactive oxygen species (ROS) (Barazzuol et al., 2021). Indeed, the physiological and signaling functions of ROS are well stablished and required to maintain cellular homeostasis; however, excessive ROS production and accumulation lead to oxidative damage of proteins, lipids and DNA (Luan et al., 2021). Excessive Ca^{2+} flux in MERCs is associated with increase of ROS production in mitochondria (Luan et al., 2021). In this way, MERCs are enriched with many regulators of redox state, which interacts with proteins and channels involved in Ca^{2+} homeostasis interfering in its flux in MERCs accordingly to the redox status of cell (Barazzuol et al., 2021). In fact, oxidoreductin-1α (Ero1α) and ER resident protein 44 (ERp44) are enriched in MERCs (Anelli et al., 2012), playing a potential role in Ca^{2+} release and traffic in MERCs in a redox-sensitive manner, and, indirectly, inducing mitochondrial ROS production. Ero1α induces the oxidation of IP_3R1, causing the dissociation of ERp44 from IP_3R1, enhancing the Ca^{2+} flux from ER to mitochondria and increasing ROS production (Anelli et al., 2012; Li et al., 2009). In basal conditions, ERp44 binds and inhibits IP_3R opening. Another important component that participates in Ca^{2+} flux in MERCs is SERCA. The SERCA pumps have diverse isoforms, including SERCA1a and 1b (found in skeletal muscle), and SERCA3 (which is less expressed). The most studied and important isoform is SERCA2b, which is the most ubiquitous pump with demonstrated higher affinity for Ca^{2+} and with an essential role in Ca^{2+} uptake (Marchi et al., 2018). This pump acts transporting Ca^{2+} from cytosol to ER lumen and, similar to IP_3R, it is also regulated by a redox-state (Krols et al., 2016). The activity of SERCA2b is stimulated by the selenoprotein N (SEPN1), which interacts with SERCA2b in a redox-sensitive manner, leading to the increase of Ca^{2+} levels in ER (Marino et al., 2015). Additionally, transmembrane chaperone calnexin (CNX) affects Ca^{2+} flux in MERCs regulating the SERCA2b redox state and the ER Ca^{2+} content, reducing the flux to mitochondria, as well as the ER-mitochondria apposition (Gutiérrez et al., 2020). On the other hand, the SERCA2b activity is inhibited by the thioredoxin-related TMX1, an ER redox-sensitive reductase, causing the increase of ER-mitochondria apposition and augmenting Ca^{2+} flux to mitochondria (Raturi et al., 2016). Additionally, glutathione peroxidase 8 (GPX8) also localizes in MERCs and regulates the ER Ca^{2+} content. Briefly, GPX8 overexpression inhibits SERCA, resulting in the decrease of Ca^{2+} in ER and, consequently, reducing ER-mitochondria Ca^{2+} flux (Yoboue et al., 2017). The role of these MERC-inserted redox components highlights the function of contact sites in maintaining the balance of mitochondrial redox state and cellular redox homeostasis (Barazzuol et al., 2021).

Besides the essential role in cellular metabolism, mitochondria are critically involved in the machinery of cell death, particularly in apoptosis, since they store many molecules that can trigger this process (Kroemer et al., 2007). While oscillations in mitochondrial Ca^{2+} are critical for maintaining mitochondrial metabolism, excessive Ca^{2+} release from the ER causes mitochondrial Ca^{2+} overload, inducing the opening of the mitochondrial permeability transition pore (mPTP) (Bonora et al., 2014; Bonora and Pinton, 2014; Giorgi et al., 2012). Notably, it has been reported that mPTP opening induces mitochondrial swelling and OMM rupture, with the consequent release of pro-apoptotic factors, such as second mitochondria-derived activator of caspases/direct inhibitor of apoptosis binding protein with low pI (SMAC/DIABLO), cytochrome *c* and apoptosis-inducing factor (AIF) into the cytosol, ultimately, triggering caspase-activating factors and initiating apoptosis (Danese et al., 2017; Kroemer et al., 2007).

MERCs and Parkinson's Disease

Increasing evidence associates MERC dysfunctions with the pathophysiology of different diseases, such as diabetes, cancer and neurodegenerative disorders (PD, AD and amyotrophic lateral sclerosis) (Cheng et al., 2020; Danese et al., 2020; Johri and Chandra, 2021; Madec et al., 2021; Sassano et al., 2017). In this scenario, MERC physiology and dysfunctions have been extensively investigated, especially in PD, since many familial PD-related proteins are associated with or have secondary functions in MERCs, such as DJ-1, PINK1, parkin and especially α-syn, the hallmark of PD pathology.

PD is a progressive neurodegenerative disorder characterized by the accumulation of α-syn in the neurons, leading to disruption of cellular Ca^{2+} homeostasis, oxidative stress, mitochondrial dysfunctions and neuronal death (Grünewald et al., 2019). Most PD cases are sporadic, but familial cases have been linked to genetic mutations in genes, referred as *PARK* genes, which encodes α-syn (*PARK1/4* or *SNCA*), parkin (*PARK2*), PINK1 (*PARK6*), DJ-1 (*PARK7*), leucine-rich-repeat kinase 2 (LRRK2, *PARK8*), ATP13A2 (*PARK9*) and other genes, such as vacuolar protein sorting-associated protein 35 gene (VPS35; *PARK17*) and vacuolar protein sorting-associated protein 13C (VPS13C, *PARK23*) (Barazzuol et al., 2020; Liu et al., 2019). Both sporadic and familial forms of PD comprise mitochondrial defects, disruption of cellular Ca^{2+} homeostasis, and impairment of the autophagic pathway, suggesting that autophagy/

mitophagy defects are a focal feature of PD pathogenesis (Krebiehl et al., 2010; Lonskaya et al., 2013; Papagiannakis et al., 2019).

In fact, PINK1 (*PARK7*) is a mitochondrial damage sensor upstream to parkin (*PARK2*), an adaptor of mitophagy. Briefly, PINK1 is rapidly and constitutively degraded under steady-state conditions in a mitochondrial membrane potential ($\Delta\Psi_m$)-dependent manner, but the loss of $\Delta\Psi_m$ stabilizes PINK1 accumulation in mitochondria. PINK1 accumulation further recruits parkin from the cytoplasm to the mitochondria with low $\Delta\Psi_m$ (Matsuda et al., 2010; Narendra et al., 2010). After recruitment, parkin mediates the engulfment of mitochondria by autophagosomes and its selective elimination (Narendra et al., 2008). Importantly, Mfn1/2 and VDAC1 located in MERCs act as targets for parkin-mediated ubiquitylation, p62/SQSTM1 recruitment and PINK1/parkin-mediated mitophagy (Geisler, Holmström, Skujat, et al., 2010; Geisler, Holmström, Treis, et al., 2010; Gu et al., 2020; Narendra et al., 2010). Overexpression of parkin in HeLa cells promotes the increase of MERCs, enhancing Ca^{2+} transfer and ATP production (Calì et al., 2013). Parkin mutations lead to its loss-of-function, and are associated to autosomal juvenile PD (Kitada et al., 1998), while PINK1 mutations affect parkin function, impairing its translocation to OMM, and, consequently, reducing mitophagy (Geisler, Holmström, Skujat, et al., 2010; Geisler, Holmström, Treis, et al., 2010).

Defective mitophagy and MERCs are also associated with LRRK2 (*PARK8*) mutations, but the specific effects of certain mutations are not completely established. Mitochondrial and ER dysfunction, as well as morphological alterations, were reported in fibroblasts derived from PD patients with the *LRRK2* R1441G or G2019S mutation. Namely, *LRRK2* G2019S mutation results in increased kinase activity and consequent overactivation of MEK/ERK pathway, leading to sustained autophagy activation and increased apoptotic hallmarks (Bravo-San Pedro et al., 2013). Moreover, the expression of LRRK2 G2019S stimulates mitochondria clearance and mitophagy via unc-51 like autophagy activating kinase 1 (ULK1) and c-Jun N-terminal kinase (JNK) dependent pathway (Zhu et al., 2013). *LRRK2* R1441G mutation, on the other hand, resulted in increased lysosomal markers associated with induction of macroautophagy, increased mitophagy and ER stress. Evidence indicates the participation of cytosolic Ca^{2+} in these processes, as these effects are partially reversed by BAPTA-AM and potentiated by MPP + insult to LRRK2 *R1441G* mutant cells (Yakhine-Diop et al., 2021). Recently, Toyofuku et al. (2020), demonstrated that LRRK2 has an effective role in MERCs formation and functions, since LRRK2 deletion resulted in reduction of contact sites and impairment of Ca^{2+} flux to mitochondria. Interestingly, the LRRK2 G2019S mutant protein, a common mutation of *PARK8* gene, had similar effects in MERC structure and functions.

As follows, the *ATP13A2* gene (*PARK9*) encodes the protein ATP13A2, a lysosomal type 5 P-type ATPase associated with familial parkinsonism. ATP13A2 is localized in lysosomes, though its mutation causes retention of the protein in the ER leading to ER stress (Ugolino et al., 2011). The analysis of fibroblasts from two patients with the L3292 and L6025 *ATP13A2* mutations showed impaired lysosomal acidification, proteolytic capacity, and diminished lysosomal-mediated clearance of autophagosomes (Dehay et al., 2012), but their association with MERC dysfunction is yet to be determined.

Likewise, associations of mutations in the VPS35 gene (*PARK17*) with PD were first described in 2008 (Wider et al., 2008), and a heterozygous missense mutation D620N was further described to be pathogenic (Kumar et al., 2018). VPS35 is part of the retromer cargo-recognition complex in the intracellular retrograde transport from endosomes to the trans-Golgi networks (Hierro et al., 2007). This mutation (D620N) results in mitochondrial fission and fragmentation, and enhanced LRRK2 kinase activity, but no motor impairments in mice (Mir et al., 2018). Thus, VPS35 is hypothesized to control LRRK2 activity and potentially causes PD through hyperactivation of LRRK2 kinase, but its relation with MERC functionality and PINK1/Parkin-mediated mitophagy is not yet elucidated.

VPS13C (*PARK23*), on the other hand, was first associated with PD in 2016 (Schreglmann and Houlden, 2016). The VPS13 gene family codifies a protein with a tubular N-terminal portion capable of solubilizing and transporting glycerolipids between membranes and has been hypothesized to have a role in the lipid exchange and organelle tethering among ER, mitochondria and other organelles (Kumar et al., 2018). Current evidence implicates different functions for VPS13 proteins in lipid transport at organelle sites. For instance, VPS13C was first localized in the OMM and its silencing resulted in lower $\Delta\Psi_m$, mitochondrial fragmentation, increased respiration rates, and exacerbated PINK1/Parkin-dependent mitophagy (Lesage et al., 2016). Additionally, VPS13C localizes to contacts of the ER with the endolysosomal system, while VPS13A was localized at ER–mitochondria contacts (Kumar et al., 2018; Park et al., 2016). These findings point out to VPS13 participation in lipid dynamics during autophagic processing together with Atg proteins.

Finally, α-syn (*PARK1/4* or *SNCA)* was the first and the most important PD-associated gene described. Mutations in *SNCA* gene lead the transcription of mutated forms of α-syn. The first mutations described, and the most studied, were the A53T and the A30P, both associated with familial forms of PD (Krüger et al., 1998; Polymeropoulos et al., 1997). These specific point mutations affect α-syn ability to bind to membranes, making it prone to form aggregates in cytoplasm when compared to wild-type (Krüger et al., 1998; McDowall and Brown, 2016; Polymeropoulos et al., 1997).

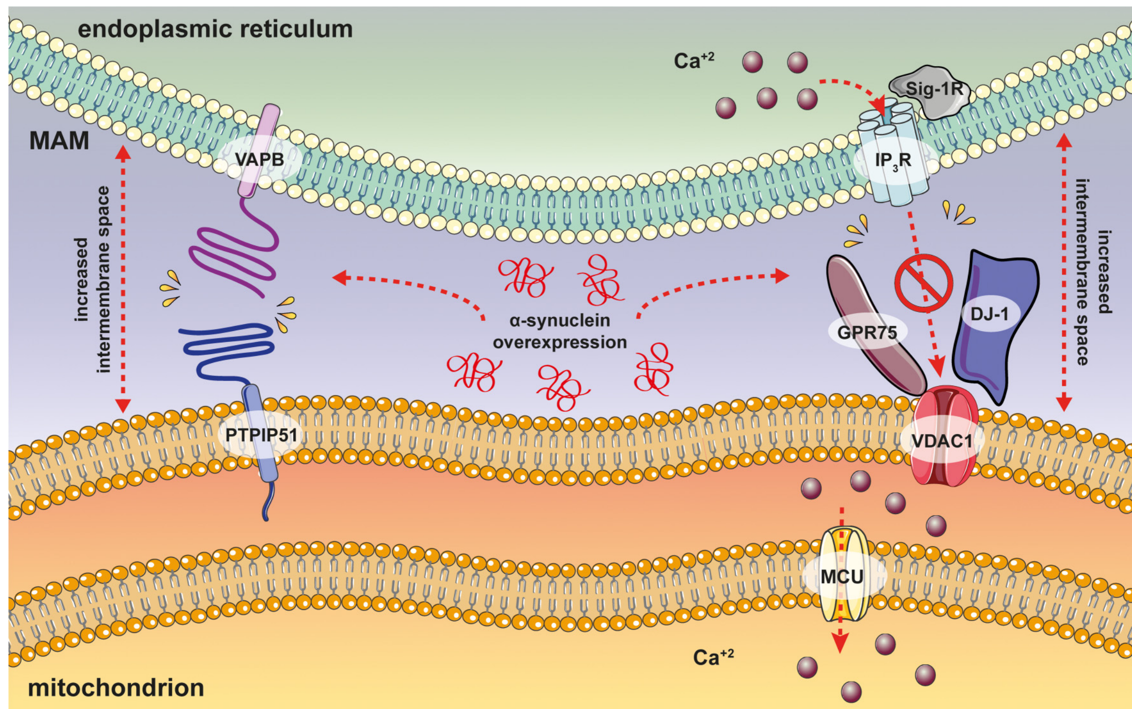

Figure 2. ER-mitochondria contact sites in α-syn overexpression. The overexpression of α-syn in cellular models leads to its accumulation in MERCs, affecting the proximity of organelles, reducing the interaction of tether complexes and MERC physiology. After reaching MERCs, α-syn interacts with VAPB in the ER membrane, disrupting the VAPB-PTPI51 interaction. α-syn overexpression also affects the interaction of IP_3R-GRP75-DJ-1-VDAC1 complex, which leads to the reduction of IP_3R-GRP75 interaction, but no change in the GRP75-VDAC1 interaction. The role of DJ-1 and its interaction in the IP_3R-GRP75-DJ-1-VDAC1 complex is not fully understood. α-syn in MERCs affects the VAPB-PTPI51 and IP_3R-GRP75-DJ-1-VDAC1 complexes, reducing ER-mitochondria interactions, increasing the gap between organelles, and drastically decreasing Ca^{2+} traffic from the ER to mitochondria. The illustration was produced using smart servier medical art vectors for publications and presentations licensed under the Creative Commons 3.0 (CC BY 3.0).

The pathogenic importance of α-syn aggregates has been extensively investigated since its accumulation is considered a key step in PD pathophysiology. For instance, α-syn may accumulate in the mitochondria and impair mitochondrial respiratory chain and Ca^{2+} homeostasis through associations with complex-I, resulting in decreased $\Delta\Psi_m$ and increased mitochondrial ROS levels (Grünewald et al., 2019; Park et al., 2020). In this regard, a new role for α-syn in PD has been debated because evidence demonstrates that apart from its cytosolic localization, it is also present in MERCs and may disrupt ER-mitochondria interaction.

In 2013, Poston et al. (2013) conducted a proteomic analysis from isolated mouse brains and detected α-syn in MERCs. This observation was corroborated by Guardia-Laguarta et al. (2014), who observed α-syn in MERCs and proposed that α-syn was specifically localized in MERCs and not in mitochondria, as previously proposed. While there is no consensus about the α-syn-induced effects in MERCs, alterations in its formation and function have been reported.

Experiments performed by Calì et al. (2012) demonstrated that the presence of α-syn in MERCs increases the number of contact sites. Moreover, α-syn increased Ca^{2+} transfer from the ER to the mitochondria, an effect reversed by its silencing. The same authors suggested that α-syn is essential to mitochondrial morphology since silenced cells displayed a fragmented mitochondrial network. Conversely, other authors demonstrated that α-syn overexpression reduced ER-mitochondria juxtaposition and impaired Ca^{2+} flux between these organelles (Erustes et al., 2021; Guardia-Laguarta et al., 2014; Paillusson et al., 2017). Additionally, experiments performed by Paillusson et al. (2017) demonstrated that α-syn binds to VAPB in the ER membrane, reducing VAPB-PTPIP51 interaction. Indeed, the interaction between VAPB and α-syn promoted the uncoupling of ER-mitochondria contacts, reducing the Ca^{2+} transfer and mitochondrial ATP production.

Our group recently assessed the role of α-syn in MERCs and explored its implications in PD pathophysiology. The overexpression of wild type (WT) α-syn and its mutant form A30P reduced the $\Delta\Psi$m and led to the accumulation of autophagy/mitophagy markers in the mitochondria (Erustes et al., 2021). Previous studies reported that α-syn-mediated $\Delta\Psi$m disruption reduces electron transport chain activity and ATP synthesis and increases mitochondrial ROS (Erustes et al., 2018; Park et al., 2018; Wang et al., 2019). Consequently, it is reasonable to assume that the

perpetuation of mitochondrial imbalances culminate in the activation of the mitochondrial cell death machinery.

Notably, the overexpression of α-syn WT or the A30P and A53T mutants in immortalized astrocytes enhanced the cellular accumulation of Bax and cell death signals (Erustes et al., 2018). In another study, transgenic animal and cellular models of α-syn overexpression revealed mitochondrial effects and increased activation of cell death pathways (Ganjam et al., 2019). Furthermore, Betzer et al. (2018) reported that α-syn interacts with SERCA pump in the ER, increasing cytosolic Ca^{2+} concentrations. Moreover, the mutations A30P and A53T affect the ability of α-syn to target MERCs, when compared to the WT α-syn (Guardia-Laguarta et al., 2014). The mechanism might be related to these mutations affecting the ability of α-syn to bind to lipid membranes (reviewed by Auluck et al., 2010).

These observations led our group to investigate the effects of α-syn overexpression in MERCs. In the experiments performed by confocal microscopy, the presence of α-syn in MERCs resulted in a reduced number of ER-mitochondria contact sites. The same study assessed whether α-syn overexpression would impair GRP75 molecular interactions with IP_3R and VDAC1 via an immunoprecipitation assay. While no alterations in the GRP75-VDAC1 interaction were detected, IP_3R-GRP75 interactions were drastically attenuated (Erustes et al., 2021). It should be pointed out that although the interaction between DJ-1 and the IP_3R-GRP75-VDAC1 complex was not evaluated in the presence of α-syn, its expression levels were not affected by α-syn overexpression. These results indicate that a disruption in the IP_3R-GRP75-VDAC1 tethering complex reduces Ca^{2+} trafficking from the ER to the mitochondria. Moreover, our group did not detect interactions between α-syn and IP_3R-GRP75-VDAC1 complex components (Figure 2). Other studies demonstrated that α-syn interacts with VDAC1 in the OMM and is translocated through the channel to the inner mitochondrial membrane, where it interacts with mitochondrial respiratory complexes and affects mitochondrial function (Rostovtseva et al., 2015; Rovini et al., 2020).

Conclusions

ER-mitochondria contact sites are dynamic and complex subcellular regions that can modulate cell metabolism and cellular processes. The most studied and prominent role of MERCs is related to Ca^{2+} signaling, promoting its trafficking between the two major Ca^{2+}-storing organelles. Additionally, MERCs play an important role in biochemical processes, such as lipid synthesis, mitochondrial shape and dynamics, autophagy/mitophagy, cellular bioenergetics, cell death, and others.

In this sense, reduction of ER-mitochondria contact sites would be expected to attenuate Ca^{2+} flux from the ER to mitochondria, disrupting many biochemical functions, especially bioenergetic and metabolic processes. Thus, understanding the interactions between neurodegeneration-related proteins and the proteins that tether these organelles and maintain this complex and intricate system is essential.

Several pieces of evidence suggest that MERCs contribute to the onset and/or progression of pathological conditions, such as neurodegenerative diseases and cancer. In PD, α-syn affects MERC physiology, disrupting tether complexes and impairing Ca^{2+} homeostasis. Additionally, it was demonstrated that α-syn accumulation and its interactions with tether complex components reduce the number of MERCs formed, as well as the Ca^{2+} traffic between ER and mitochondria. On the other hand, evidence points to opposite effects of α-syn overexpression in MERCs, as it has an important role in mitochondrial morphology, and it promotes the increase of ER-mitochondria juxtaposition and Ca^{2+} flux (Calì et al., 2012). The discrepancies about the role of α-syn in MERCs could be related to its levels of expression, as proposed by Calì et al., (2019), because the effect of α-syn is dose-dependent, and high levels lead to loss of effects in MERCs. However, further studies are essential to better understand the α-syn-mediated effects in this region.

Our description of several factors that regulate and coordinate the functions of ER-mitochondria contact sites, makes it clear that the identification of other regulatory complexes will be an important step to understanding of the nature and function of MERCs. Future studies searching for molecules that can modulate MERC functions could provide valuable insights into PD physiopathology and other pathologies associated with impaired Ca^{2+} homeostasis in the ER and/or mitochondria, as well as their contact sites.

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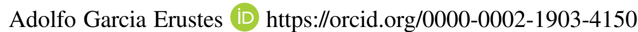
Adolfo Garcia Erustes  https://orcid.org/0000-0002-1903-4150

References

Anelli, T., Bergamelli, L., Margittai, E., Rimessi, A., Fagioli, C., Malgaroli, A., Pinton, P., Ripamonti, M., Rizzuto, R., & Sitia, R. (2012). Ero1α regulates Ca(2+) fluxes at the endoplasmic reticulum-mitochondria interface (MAM). *Antioxidants & Redox Signaling*, *16*(10), 1077–1087. https://doi.org/10.1089/ars.2011.4004

Auluck, P. K., Caraveo, G., & Lindquist, S. (2010). α-Synuclein: Membrane interactions and toxicity in Parkinson's disease. *Annual Review of Cell and Developmental Biology*, *26*(1), 211–233. https://doi.org/10.1146/annurev.cellbio.042308.113313

Barazzuol, L., Giamogante, F., Brini, M., & Calì, T. (2020). PINK1/Parkin Mediated mitophagy, ca. *International Journal of Molecular Sciences*, *21*(5), 1772. https://doi.org/10.3390/ijms21051772

Barazzuol, L., Giamogante, F., & Calì, T. (2021). Mitochondria associated membranes (MAMs): Architecture and physiopathological role. *Cell Calcium*, *94*, 102343. https://doi.org/10.1016/j.ceca.2020.102343

Bartok, A., Weaver, D., Golenár, T., Nichtova, Z., Katona, M., Bánsághi, S., Alzayady, K. J., Thomas, V. K., Ando, H., Mikoshiba, K., Joseph, S. K., Yule, D. I., Csordás, G., & Hajnóczky, G. (2019). IP3receptor Isoforms differently regulate ER-mitochondrial contacts and local calcium transfer. *Nature Communications*, *10*(1), 3726. https://doi.org/10.1038/s41467-019-11646-3

Basso, V., Marchesan, E., & Ziviani, E. (2020). A trio has turned into a quartet: DJ-1 interacts with the IP3R-Grp75-VDAC complex to control ER-mitochondria interaction. *Cell Calcium*, *87*, 102186. https://doi.org/10.1016/j.ceca.2020.102186

Belosludtsev, K. N., Dubinin, M. V., Belosludtseva, N. V., & Mironova, G. D. (2019). Mitochondrial Ca2+transport: Mechanisms, molecular structures, and role in cells. *Biochemistry (Moscow)*, *84*(6), 593–607. https://doi.org/10.1134/S0006297919060026

Betzer, C., Lassen, L. B., Olsen, A., Kofoed, R. H., Reimer, L., Gregersen, E., Zheng, J., Calì, T., Gai, W. P., Chen, T., Moeller, A., Brini, M., Fu, Y., Halliday, G., Brudek, T., Aznar, S., Pakkenberg, B., Andersen, J. P., & Jensen, P. H. (2018). Alpha-synuclein aggregates activate calcium pump SERCA leading to calcium dysregulation. *EMBO Reports*, *19*(5). https://doi.org/10.15252/embr.201744617

Bonora, M., Bravo-San Pedro, J. M., Kroemer, G., Galluzzi, L., & Pinton, P. (2014). Novel insights into the mitochondrial permeability transition. *Cell Cycle*, *13*(17), 2666–2670. https://doi.org/10.4161/15384101.2014.949082

Bonora, M., & Pinton, P. (2014). The mitochondrial permeability transition pore and cancer: Molecular mechanisms involved in cell death. *Frontiers in Oncology*, *4*, 302. https://doi.org/10.3389/fonc.2014.00302

Borsche, M., Pereira, S. L., Klein, C., & Grünewald, A. (2021). Mitochondria and Parkinson's disease: Clinical, molecular, and translational aspects. *Journal of Parkinson's Disease*, *11*(1), 45–60. https://doi.org/10.3233/JPD-201981

Bravo-San Pedro, J. M., Niso-Santano, M., Gómez-Sánchez, R., Pizarro-Estrella, E., Aiastui-Pujana, A., Gorostidi, A., Climent, V., de Maturana R, L., Sanchez-Pernaute, R., de Munain A, L., Fuentes, J. M., & González-Polo, R. A. (2013). The LRRK2 G2019S mutant exacerbates basal autophagy through activation of the MEK/ERK pathway. *Cellular and Molecular Life Sciences*, *70*(1), 121–136. https://doi.org/10.1007/s00018-012-1061-y

Brobeil, A., Dietel, E., Gattenlöhner, S., & Wimmer, M. (2017). Orchestrating cellular signaling pathways-the cellular "conductor" protein tyrosine phosphatase interacting protein 51 (PTPIP51). *Cell and Tissue Research*, *368*(3), 411–423. https://doi.org/10.1007/s00441-016-2508-5

Calì, T., Ottolini, D., Negro, A., & Brini, M. (2012). α-Synuclein controls mitochondrial calcium homeostasis by enhancing endoplasmic reticulum-mitochondria interactions. *Journal of Biological Chemistry*, *287*(22), 17914–17929. https://doi.org/10.1074/jbc.M111.302794

Calì, T., Ottolini, D., Negro, A., & Brini, M. (2013). Enhanced parkin levels favor ER-mitochondria crosstalk and guarantee Ca(2+) transfer to sustain cell bioenergetics. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1832*(4), 495–508. https://doi.org/10.1016/j.bbadis.2013.01.004

Calì, T., Ottolini, D., Vicario, M., Catoni, C., Vallese, F., Cieri, D., Barazzuol, L., & Brini, M. (2019). splitGFP technology reveals dose-dependent ER-mitochondria interface modulation by α-synuclein A53T and A30P mutants. *Cells*, *8*(9). https://doi.org/10.3390/cells8091072

Chandra, D., Choy, G., Deng, X., Bhatia, B., Daniel, P., & Tang, D. G. (2004). Association of active caspase 8 with the mitochondrial membrane during apoptosis: Potential roles in cleaving BAP31 and caspase 3 and mediating mitochondrion-endoplasmic reticulum cross talk in etoposide-induced cell death. *Molecular and Cellular Biology*, *24*(15), 6592–6607. https://doi.org/10.1128/MCB.24.15.6592-6607.2004

Cheng, H., Gang, X., He, G., Liu, Y., Wang, Y., Zhao, X., & Wang, G. (2020). The molecular mechanisms underlying mitochondria-associated endoplasmic Reticulum membrane-induced insulin resistance. *Frontiers in Endocrinology*, *11*, 592129. https://doi.org/10.3389/fendo.2020.592129

Csordás, G., Renken, C., Várnai, P., Walter, L., Weaver, D., Buttle, K. F., Balla, T., Mannella, C. A., & Hajnóczky, G. (2006). Structural and functional features and significance of the physical linkage between ER and mitochondria. *Journal of Cell Biology*, *174*, 915–921. https://doi.org/10.1083/jcb.200604016

Danese, A., Marchi, S., Vitto, V. A. M., Modesti, L., Leo, S., Wieckowski, M. R., Giorgi, C., & Pinton, P. (2020). Cancer-Related increases and decreases in calcium signaling at the endoplasmic Reticulum-mitochondria interface (MAMs). *Reviews of Physiology Biochemistry and Pharmacology*. https://doi.org/10.1007/112_2020_43

Danese, A., Patergnani, S., Bonora, M., Wieckowski, M. R., Previati, M., Giorgi, C., & Pinton, P. (2017). Calcium regulates cell death in cancer: Roles of the mitochondria and mitochondria-associated membranes (MAMs). *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, *1858*(8), 615–627. https://doi.org/10.1016/j.bbabio.2017.01.003

de Brito, O. M., & Scorrano, L. (2008). Mitofusin 2 tethers endoplasmic reticulum to mitochondria. *Nature*, *456*(7222), 605–610. https://doi.org/10.1038/nature07534

Dehay, B., Ramirez, A., Martinez-Vicente, M., Perier, C., Canron, M. H., Doudnikoff, E., Vital, A., Vila, M., Klein, C., & Bezard, E. (2012). Loss of P-type ATPase ATP13A2/PARK9 function induces general lysosomal deficiency and leads to

Parkinson disease neurodegeneration. *Proceedings of the National Academy of Sciences*, *109*(24), 9611–9616. https://doi.org/10.1073/pnas.1112368109

D'Eletto, M., Rossin, F., Occhigrossi, L., Farrace, M. G., Faccenda, D., Desai, R., Marchi, S., Refolo, G., Falasca, L., Antonioli, M., Ciccosanti, F., Fimia, G. M., Pinton, P., Campanella, M., & Piacentini, M. (2018). Transglutaminase type 2 regulates ER-mitochondria contact sites by interacting with GRP75. *Cell Reports*, *25*(13), 3573–3581.e4. https://doi.org/10.1016/j.celrep.2018.11.094

Detmer, S. A., & Chan, D. C. (2007). Functions and dysfunctions of mitochondrial dynamics. *Nature Reviews Molecular Cell Biology*, *8*(11), 870–879. https://doi.org/10.1038/nrm2275

Dorn, G. W. (2020). Mitofusins as mitochondrial anchors and tethers. *Journal of Molecular and Cellular Cardiology*, *142*, 146–153. https://doi.org/10.1016/j.yjmcc.2020.04.016

Erustes, A. G., D'Eletto, M., Guarache, G. C., Ureshino, R. P., Bincoletto, C., da Silva Pereira, G. J., Piacentini, M., & Smaili, S. S. (2021). Overexpression of α-synuclein inhibits mitochondrial Ca^{2+} trafficking between the endoplasmic reticulum and mitochondria through MAMs by altering the GRP75-IP3R interaction. *Journal of Neuroscience Research, 99*(11), 2932–2947. https://doi.org/10.1002/jnr.24952

Erustes, A. G., Stefani, F. Y., Terashima, J. Y., Stilhano, R. S., Monteforte, P. T., da Silva Pereira, G. J., Han, S. W., Calgarotto, A. K., Hsu, Y. T., Ureshino, R. P., Bincoletto, C., & Smaili, S. S. (2018). Overexpression of α-synuclein in an astrocyte cell line promotes autophagy inhibition and apoptosis. *Journal of Neuroscience Research*, *96*(1), 160–171. https://doi.org/10.1002/jnr.24092

Filadi, R., Greotti, E., Turacchio, G., Luini, A., Pozzan, T., & Pizzo, P. (2016). Presenilin 2 modulates endoplasmic Reticulum-mitochondria coupling by tuning the antagonistic effect of mitofusin 2. *Cell Reports*, *15*(10), 2226–2238. https://doi.org/10.1016/j.celrep.2016.05.013

Filadi, R., Pendin, D., & Pizzo, P. (2018). Mitofusin 2: From functions to disease. *Cell Death & Disease*, *9*(3), 330. https://doi.org/10.1038/s41419-017-0023-6

Fujimoto, M., & Hayashi, T. (2011). New insights into the role of mitochondria-associated endoplasmic reticulum membrane. *International Review of Cell and Molecular Biology*, *292*, 73–117. https://doi.org/10.1016/B978-0-12-386033-0.00002-5

Galluzzi, L., Kepp, O., & Kroemer, G. (2012). Mitochondria: Master regulators of danger signalling. *Nature Reviews Molecular Cell Biology*, *13*(12), 780–788. https://doi.org/10.1038/nrm3479

Ganjam, G. K., Bolte, K., Matschke, L. A., Neitemeier, S., Dolga, A. M., Höllerhage, M., Höglinger, G. U., Adamczyk, A., Decher, N., Oertel, W. H., & Culmsee, C. (2019). Mitochondrial damage by α-synuclein causes cell death in human dopaminergic neurons. *Cell Death & Disease*, *10*(11), 865. https://doi.org/10.1038/s41419-019-2091-2

Gao, P., Yang, W., & Sun, L. (2020). Mitochondria-Associated endoplasmic Reticulum membranes (MAMs) and their prospective roles in kidney disease. *Oxidative Medicine and Cellular Longevity*, *2020*, 1–21. https://doi.org/10.1155/2020/3120539

Geisler, S., Holmström, K. M., Skujat, D., Fiesel, F. C., Rothfuss, O. C., Kahle, P. J., & Springer, W. (2010a). PINK1/Parkin-mediated Mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nature Cell Biology*, *12*(2), 119–131. https://doi.org/10.1038/ncb2012

Geisler, S., Holmström, K. M., Treis, A., Skujat, D., Weber, S. S., Fiesel, F. C., Kahle, P. J., & Springer, W. (2010b). The PINK1/parkin-mediated mitophagy is compromised by PD-associated mutations. *Autophagy*, *6*(7), 871–878. https://doi.org/10.4161/auto.6.7.13286

Gellerich, F. N., Gizatullina, Z., Trumbeckaite, S., Nguyen, H. P., Pallas, T., Arandarcikaite, O., Vielhaber, S., Seppet, E., & Striggow, F. (2010). The regulation of OXPHOS by extramitochondrial calcium. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, *1797*(6–7), 1018–1027. https://doi.org/10.1016/j.bbabio.2010.02.005

Gelmetti, V., De Rosa, P., Torosantucci, L., Marini, E. S., Romagnoli, A., Di Rienzo, M., Arena, G., Vignone, D., Fimia, G. M., & Valente, E. M. (2017). PINK1 And BECN1 relocalize at mitochondria-associated membranes during mitophagy and promote ER-mitochondria tethering and autophagosome formation. *Autophagy*, *13*(4), 654–669. https://doi.org/10.1080/15548627.2016.1277309

Giorgi, C., Baldassari, F., Bononi, A., Bonora, M., De Marchi, E., Marchi, S., Missiroli, S., Patergnani, S., Rimessi, A., Suski, J. M., Wieckowski, M. R., & Pinton, P. (2012). Mitochondrial Ca(2+) and apoptosis. *Cell Calcium*, *52*(1), 36–43. https://doi.org/10.1016/j.ceca.2012.02.008

Giorgi, C., Marchi, S., & Pinton, P. (2018). The machineries, regulation and cellular functions of mitochondrial calcium. *Nature Reviews Molecular Cell Biology*, *19*(11), 713–730. https://doi.org/10.1038/s41580-018-0052-8

Gomez-Suaga, P., Paillusson, S., Stoica, R., Noble, W., Hanger, D. P., & Miller, C. C. J. (2017). The ER-mitochondria tethering Complex VAPB-PTPIP51 regulates autophagy. *Current Biology*, *27*(3), 371–385. https://doi.org/10.1016/j.cub.2016.12.038

Grünewald, A., Kumar, K. R., & Sue, C. M. (2019). New insights into the complex role of mitochondria in Parkinson's disease. *Progress in Neurobiology*, *177*, 73–93. https://doi.org/10.1016/j.pneurobio.2018.09.003

Gu, J., Zhang, T., Guo, J., Chen, K., Li, H., & Wang, J. (2020). PINK1 Activation and translocation to mitochondria-associated membranes mediates mitophagy and protects against hepatic ischemia/reperfusion injury. *Shock (Augusta, Ga.)*, *54*(6), 783–793. https://doi.org/10.1097/SHK.0000000000001534

Guardia-Laguarta, C., Area-Gomez, E., Rüb, C., Liu, Y., Magrané, J., Becker, D., Voos, W., Schon, E. A., & Przedborski, S. (2014). α-Synuclein is localized to mitochondria-associated ER membranes. *Journal of Neuroscience*, *34*(1), 249–259. https://doi.org/10.1523/JNEUROSCI.2507-13.2014

Gutiérrez, T., Qi, H., Yap, M. C., Tahbaz, N., Milburn, L. A., Lucchinetti, E., Lou, P. H., Zaugg, M., LaPointe, P. G., Mercier, P.l, Overduin, M., Bischof, H., Burgstaller, S., Malli, R., Ballanyi, K., Shuai, J., & Simmen, T. (2020). The ER chaperone calnexin controls mitochondrial positioning and respiration. *Science Signaling*, *13*(638). https://doi.org/10.1126/scisignal.aax6660

Hamasaki, M., Shibutani, S. T., & Yoshimori, T. (2013). Up-to-date membrane biogenesis in the autophagosome formation. *Current Opinion in Cell Biology*, *25*(4), 455–460. https://doi.org/10.1016/j.ceb.2013.03.004

Hayashi, T., Rizzuto, R., Hajnoczky, G., & Su, T. P. (2009). MAM: More than just a housekeeper. *Trends in Cell Biology*, *19*(2), 81–88. https://doi.org/10.1016/j.tcb.2008.12.002

Hayashi, T., & Su, T. P. (2007). Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. *Cell*, *131*(3), 596–610. https://doi.org/10.1016/j.cell.2007.08.036

Hierro, A., Rojas, A. L., Rojas, R., Murthy, N., Effantin, G., Kajava, A. V., Steven, A. C., Bonifacino, J. S., & Hurley, J. H. (2007). Functional architecture of the retromer cargo-recognition complex. *Nature*, *449*(7165), 1063–1067. https://doi.org/10.1038/nature06216

Iwasawa, R., Mahul-Mellier, A. L., Datler, C., Pazarentzos, E., & Grimm, S. (2011). Fis1 and Bap31 bridge the mitochondria-ER interface to establish a platform for apoptosis induction. *The EMBO Journal*, *30*(3), 556–568. https://doi.org/10.1038/emboj.2010.346

Ji, W. K., Chakrabarti, R., Fan, X., Schoenfeld, L., Strack, S., & Higgs, H. N. (2017). Receptor-mediated Drp1 oligomerization on endoplasmic reticulum. *Journal of Cell Biology*, *216*(12), 4123–4139. https://doi.org/10.1083/jcb.201610057

Johri, A., & Chandra, A. (2021). Connection lost, MAM: Errors in ER-mitochondria connections in neurodegenerative diseases. *Brain Sciences*, *11*(11), 1437. https://doi.org/10.3390/brainsci11111437

Kerkhofs, M., Bittremieux, M., Morciano, G., Giorgi, C., Pinton, P., Parys, J. B., & Bultynck, G. (2018). Emerging molecular mechanisms in chemotherapy: Ca^{2+} signaling at the mitochondria-associated endoplasmic reticulum membranes. *Cell Death & Disease*, *9*(3), 334. https://doi.org/10.1038/s41419-017-0179-0

Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y., & Shimizu, N. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature*, *392*(6676), 605–608. https://doi.org/10.1038/33416

Krebiehl, G., Ruckerbauer, S., Burbulla, L. F., Kieper, N., Maurer, B., Waak, J., Wolburg, H., Gizatullina, Z., Gellerich, F. N., Woitalla, D., Riess, O., Kahle, P. J., Proikas-Cezanne, T., Krüger, R., & Petrucelli, L. (2010). Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1. *PLoS One*, *5*(2), e9367. https://doi.org/10.1371/journal.pone.0009367

Kroemer, G., Galluzzi, L., & Brenner, C. (2007). Mitochondrial membrane permeabilization in cell death. *Physiological Reviews*, *87*(1), 99–163. https://doi.org/10.1152/physrev.00013.2006

Krols, M., Bultynck, G., & Janssens, S. (2016). ER-Mitochondria contact sites: A new regulator of cellular calcium flux comes into play. *Journal of Cell Biology*, *214*(4), 367–370. https://doi.org/10.1083/jcb.201607124

Krüger, R., Kuhn, W., Müller, T., Woitalla, D., Graeber, M., Kösel, S., Przuntek, H., Epplen, J. T., Schöls, L., & Riess, O. (1998). Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nature Genetics*, *18*(2), 106–108. https://doi.org/10.1038/ng0298-106

Kumar, N., Leonzino, M., Hancock-Cerutti, W., Horenkamp, F. A., Li, P., Lees, J. A., Wheeler, H., Reinisch, K. M., & De Camilli, P. (2018). VPS13A And VPS13C are lipid transport proteins differentially localized at ER contact sites. *Journal of Cell Biology*, *217*(10), 3625–3639. https://doi.org/10.1083/jcb.201807019

Leal, N. S., Schreiner, B., Pinho, C. M., Filadi, R., Wiehager, B., Karlström, H., Pizzo, P., & Ankarcrona, M. (2016). Mitofusin-2 knockdown increases ER-mitochondria contact and decreases amyloid β-peptide production. *Journal of Cellular and Molecular Medicine*, *20*(9), 1686–1695. https://doi.org/10.1111/jcmm.12863

Lee, J. E., Westrate, L. M., Wu, H., Page, C., & Voeltz, G. K. (2016). Multiple dynamin family members collaborate to drive mitochondrial division. *Nature*, *540*(7631), 139–143. https://doi.org/10.1038/nature20555

Lesage, S., Drouet, V., Majounie, E., Deramecourt, V., Jacoupy, M., Nicolas, A., Cormier-Dequaire, F., Hassoun, S. M., Pujol, C., Ciura, S., Erpapazoglou, Z., Usenko, T., Maurage, C.-A., Sahbatou, M., Liebau, S., Ding, J., Bilgic, B., Emre, M., Erginel-Unaltuna, N., … Brice, A. (2016). Loss of VPS13C function in autosomal-recessive parkinsonism causes mitochondrial dysfunction and increases PINK1/parkin-dependent mitophagy. *The American Journal of Human Genetics*, *98*(3), 500–513. https://doi.org/10.1016/j.ajhg.2016.01.014

Lewin, T. M., Kim, J. H., Granger, D. A., Vance, J. E., & Coleman, R. A. (2001). Acyl-CoA synthetase isoforms 1, 4, and 5 are present in different subcellular membranes in rat liver and can be inhibited independently. *Journal of Biological Chemistry*, *276*(27), 24674–24679. https://doi.org/10.1074/jbc.M102036200

Li, G., Mongillo, M., Chin, K. T., Harding, H., Ron, D., Marks, A. R., & Tabas, I. (2009). Role of ERO1–alpha-mediated stimulation of inositol 1,4,5-triphosphate receptor activity in endoplasmic reticulum stress-induced apoptosis. *Journal of Cell Biology*, *186*(6), 783–792. https://doi.org/10.1083/jcb.200904060

Liu, Y., Ma, X., Fujioka, H., Liu, J., Chen, S., & Zhu, X. (2019). DJ-1 regulates the integrity and function of ER-mitochondria association through interaction with IP3R3-Grp75-VDAC1. *Proceedings of the National Academy of Sciences*, *116*(50), 25322–25328. https://doi.org/10.1073/pnas.1906565116

Lonskaya, I., Hebron, M. L., Algarzae, N. K., Desforges, N., & Moussa, C. E. (2013). Decreased parkin solubility is associated with impairment of autophagy in the nigrostriatum of sporadic Parkinson's disease. *Neuroscience*, *232*, 90–105. https://doi.org/10.1016/j.neuroscience.2012.12.018

Luan, Y., Yuan, R. X., Feng, Q., Chen, X., & Yang, Y. (2021). Structure and function of mitochondria-associated endoplasmic Reticulum membranes (MAMs) and their role in cardiovascular diseases. *Oxidative Medicine and Cellular Longevity*, *2021*, 1–19. https://doi.org/10.1155/2021/4578809

Lv, Y., Li, Y., Zhang, D., Zhang, A., Guo, W., & Zhu, S. (2018). HMGB1-induced Asthmatic airway inflammation through GRP75-mediated enhancement of ER-mitochondrial ca. *Journal of Cellular Biochemistry*, *119*(5), 4205–4215. https://doi.org/10.1002/jcb.26653

Madec, A. M., Perrier, J., Panthu, B., & Dingreville, F. (2021). Role of mitochondria-associated endoplasmic reticulum membrane (MAMs) interactions and calcium exchange in the development of type 2 diabetes. *International Review of Cell and Molecular Biology*, *363*, 169–202. https://doi.org/10.1016/bs.ircmb.2021.06.001

Marchi, S., Giorgi, C., Oparka, M., Duszynski, J., Wieckowski, M. R., & Pinton, P. (2014). Oncogenic and oncosuppressive signal transduction at mitochondria-associated endoplasmic reticulum membranes. *Molecular & Cellular Oncology*, *1*(2), e956469. https://doi.org/10.4161/23723548.2014.956469

Marchi, S., Patergnani, S., Missiroli, S., Morciano, G., Rimessi, A., Wieckowski, M. R., Giorgi, C., & Pinton, P. (2018). Mitochondrial and endoplasmic reticulum calcium homeostasis and cell death. *Cell Calcium*, *69*, 62–72. https://doi.org/10.1016/j.ceca.2017.05.003

Marino, M., Stoilova, T., Giorgi, C., Bachi, A., Cattaneo, A., Auricchio, A., Pinton, P., & Zito, E. (2015). SEPN1, An endoplasmic reticulum-localized selenoprotein linked to skeletal muscle pathology, counteracts hyperoxidation by means of redox-regulating SERCA2 pump activity. *Human Molecular Genetics*, *24*(7), 1843–1855. https://doi.org/10.1093/hmg/ddu602

Matsuda, N., Sato, S., Shiba, K., Okatsu, K., Saisho, K., Gautier, C. A., Sou, Y. S., Saiki, S., Kawajiri, S., Sato, F., Kimura, M., Komatsu, M., Hattori, N., & Tanaka, K. (2010). PINK1 Stabilized by mitochondrial depolarization recruits parkin to damaged mitochondria and activates latent parkin for mitophagy. *Journal of Cell Biology*, *189*(2), 211–221. https://doi.org/10.1083/jcb.200910140

McDowall, J. S., & Brown, D. R. (2016). Alpha-synuclein: Relating metals to structure, function and inhibition. *Metallomics: Integrated Biometal Science*, *8*(4), 385–397. https://doi.org/10.1039/c6mt00026f

Mencke, P., Boussaad, I., Romano, C. D., Kitami, T., Linster, C. L., & Krüger, R. (2021). The role of DJ-1 in cellular metabolism and pathophysiological implications for Parkinson's disease. *Cells*, *10*(2), 347. https://doi.org/10.3390/cells10020347

Mendes, C. C., Gomes, D. A., Thompson, M., Souto, N. C., Goes, T. S., Goes, A. M., Rodrigues, M. A., Gomez, M. V., Nathanson, M. H., & Leite, M. F. (2005). The type III inositol 1,4,5–trisphosphate receptor preferentially transmits apoptotic Ca^{2+} signals into mitochondria. *Journal of Biological Chemistry*, *280*(49), 40892–40900. https://doi.org/10.1074/jbc.M506623200

Mir, R., Tonelli, F., Lis, P., Macartney, T., Polinski, N. K., Martinez, T. N., Chou, M. Y., Howden, A. J. M., König, T., Hotzy, C., Milenkovic, I., Brücke, T., Zimprich, A., Sammler, E., & Alessi, D. R. (2018). The Parkinson's disease VPS35[D620N] mutation enhances LRRK2-mediated rab protein phosphorylation in mouse and human. *Biochemical Journal*, *475*(11), 1861–1883. https://doi.org/10.1042/BCJ20180248

Mizushima, N., & Komatsu, M. (2011). Autophagy: Renovation of cells and tissues. *Cell*, *147*(4), 728–741. https://doi.org/10.1016/j.cell.2011.10.026

Morciano, G., Marchi, S., Morganti, C., Sbano, L., Bittremieux, M., Kerkhofs, M., Corricelli, M., Danese, A., Karkucinska-Wieckowska, A., Wieckowski, M. R., Bultynck, G., Giorgi, C., & Pinton, P. (2018). Role of mitochondria-associated ER membranes in calcium regulation in cancer-specific settings. *Neoplasia (New York, N.Y.)*, *20*(5), 510–523. https://doi.org/10.1016/j.neo.2018.03.005

Naon, D., Zaninello, M., Giacomello, M., Varanita, T., Grespi, F., Lakshminaranayan, S., Serafini, A., Semenzato, M., Herkenne, S., Hernández-Alvarez, M. I., Zorzano, A., De Stefani, D., Dorn, G. W., & Scorrano, L. (2016). Critical reappraisal confirms that mitofusin 2 is an endoplasmic reticulum-mitochondria tether. *Proceedings of the National Academy of Sciences*, *113*(40), 11249–11254. https://doi.org/10.1073/pnas.1606786113

Narendra, D., Tanaka, A., Suen, D. F., & Youle, R. J. (2008). Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *Journal of Cell Biology*, *183*(5), 795–803. https://doi.org/10.1083/jcb.200809125

Narendra, D. P., Jin, S. M., Tanaka, A., Suen, D. F., Gautier, C. A., Shen, J., Cookson, M. R., & Youle, R. J. (2010). PINK1 Is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biology*, *8*(1), e1000298. https://doi.org/10.1371/journal.pbio.1000298

Orrenius, S., Zhivotovsky, B., & Nicotera, P. (2003). Regulation of cell death: The calcium-apoptosis link. *Nature Reviews Molecular Cell Biology*, *4*(7), 552–565. https://doi.org/10.1038/nrm1150

Ottolini, D., Calì, T., Negro, A., & Brini, M. (2013). The Parkinson disease-related protein DJ-1 counteracts mitochondrial impairment induced by the tumour suppressor protein p53 by enhancing endoplasmic reticulum-mitochondria tethering. *Human Molecular Genetics*, *22*(11), 2152–2168. https://doi.org/10.1093/hmg/ddt068

Paillusson, S., Gomez-Suaga, P., Stoica, R., Little, D., Gissen, P., Devine, M. J., Noble, W., Hanger, D. P., & Miller, C. C. J. (2017). α-Synuclein binds to the ER–mitochondria tethering protein VAPB to disrupt Ca^{2+} homeostasis and mitochondrial ATP production. *Acta Neuropathologica*, *134*(1), 129–149. https://doi.org/10.1007/s00401-017-1704-z

Papagiannakis, N., Xilouri, M., Koros, C., Simitsi, A. M., Stamelou, M., Maniati, M., & Stefanis, L. (2019). Autophagy dysfunction in peripheral blood mononuclear cells of Parkinson's disease patients. *Neuroscience Letters*, *704*, 112–115. https://doi.org/10.1016/j.neulet.2019.04.003

Park, J. H., Burgess, J. D., Faroqi, A. H., DeMeo, N. N., Fiesel, F. C., Springer, W., Delenclos, M., & McLean, P. J. (2020). Alpha-synuclein-induced mitochondrial dysfunction is mediated via a sirtuin 3-dependent pathway. *Molecular Neurodegeneration*, *15*(1), 5. https://doi.org/10.1186/s13024-019-0349-x

Park, J. S., Davis, R. L., & Sue, C. M. (2018). Mitochondrial dysfunction in Parkinson's disease: New mechanistic insights and therapeutic perspectives. *Current Neurology and Neuroscience Reports*, *18*(5), 21. https://doi.org/10.1007/s11910-018-0829-3

Park, J. S., Thorsness, M. K., Policastro, R., McGoldrick, L. L., Hollingsworth, N. M., Thorsness, P. E., & Neiman, A. M. (2016). Yeast Vps13 promotes mitochondrial function and is localized at membrane contact sites. *Molecular Biology of the Cell*, *27*(15), 2435–2449. https://doi.org/10.1091/mbc.E16-02-0112

Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E. S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W. G., Lazzarini, A. M., Duvoisin, R. C., Di Iorio, G., Golbe, L. I., & Nussbaum, R. L. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science (New York, N.Y.)*, *276*(5321), 2045–2047. https://doi.org/10.1126/science.276.5321.2045

Poston, C. N., Krishnan, S. C., & Bazemore-Walker, C. R. (2013). In-depth proteomic analysis of mammalian mitochondria-associated membranes (MAM). *Journal of Proteomics*, *79*, 219–230. https://doi.org/10.1016/j.jprot.2012.12.018

Raturi, A., Gutiérrez, T., Ortiz-Sandoval, C., Ruangkittisakul, A., Herrera-Cruz, M. S., Rockley, J. P., Gesson, K., Ourdev, D., Lou, P. H., Lucchinetti, E., Tahbaz, N., Zaugg, M., Baksh, S., Ballanyi, K., & Simmen, T. (2016). TMX1 Determines cancer cell metabolism as a thiol-based modulator of ER-mitochondria Ca^{2+} flux. *Journal of Cell Biology*, *214*(4), 433–444. https://doi.org/10.1083/jcb.201512077

Rizzuto, R., Marchi, S., Bonora, M., Aguiari, P., Bononi, A., De Stefani, D., Giorgi, C., Leo, S., Rimessi, A., Siviero, R., Zecchini, E., & Pinton, P. (2009). Ca(2+) transfer from the ER to mitochondria: When, how and why. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, *1787*(11), 1342–1351. https://doi.org/10.1016/j.bbabio.2009.03.015

Rizzuto, R., Pinton, P., Carrington, W., Fay, F. S., Fogarty, K. E., Lifshitz, L. M., Tuft, R. A., & Pozzan, T. (1998). Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca^{2+} responses. *Science (New York, N.Y.)*, *280*(5370), 1763–1766. https://doi.org/10.1126/science.280.5370.1763

Rossi, A., Pizzo, P., & Filadi, R. (2019). Calcium, mitochondria and cell metabolism: A functional triangle in bioenergetics. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, *1866*(7), 1068–1078. https://doi.org/10.1016/j.bbamcr.2018.10.016

Rossin, F., D'Eletto, M., Falasca, L., Sepe, S., Cocco, S., Fimia, G. M., Campanella, M., Mastroberardino, P. G., Farrace, M. G., & Piacentini, M. (2015). Transglutaminase 2 ablation leads to mitophagy impairment associated with a metabolic shift towards aerobic glycolysis. *Cell Death & Differentiation*, *22*(3), 408–418. https://doi.org/10.1038/cdd.2014.106

Rostovtseva, T. K., Gurnev, P. A., Protchenko, O., Hoogerheide, D. P., Yap, T. L., Philpott, C. C., Lee, J. C., & Bezrukov, S. M. (2015). α-Synuclein shows high affinity interaction with voltage-dependent anion channel, suggesting mechanisms of mitochondrial regulation and toxicity in Parkinson disease. *Journal of Biological Chemistry*, *290*(30), 18467–18477. https://doi.org/10.1074/jbc.M115.641746

Rovini, A., Gurnev, P. A., Beilina, A., Queralt-Martín, M., Rosencrans, W., Cookson, M. R., Bezrukov, S. M., & Rostovtseva, T. K. (2020). Molecular mechanism of olesoxime-mediated neuroprotection through targeting α-synuclein interaction with mitochondrial VDAC. *Cellular and Molecular Life Sciences*, *77*(18), 3611–3626. https://doi.org/10.1007/s00018-019-03386-w

Ryskamp, D. A., Korban, S., Zhemkov, V., Kraskovskaya, N., & Bezprozvanny, I. (2019). Neuronal Sigma-1 receptors: Signaling functions and protective roles in neurodegenerative diseases. *Frontiers in Neuroscience*, *13*, 862. https://doi.org/10.3389/fnins.2019.00862

Sassano, M. L., van Vliet, A. R., & Agostinis, P. (2017). Mitochondria-Associated membranes as networking platforms and regulators of cancer cell fate. *Frontiers in Oncology*, *7*, 174. https://doi.org/10.3389/fonc.2017.00174

Schapira, A. H., Cooper, J. M., Dexter, D., Jenner, P., Clark, J. B., & Marsden, C. D. (1989). Mitochondrial complex I deficiency in Parkinson's disease. *The Lancet*, *333*(8649), 1269. https://doi.org/10.1016/S0140-6736(89)92366-0

Schreglmann, S. R., & Houlden, H. (2016). VPS13C-Another Hint at mitochondrial dysfunction in familial Parkinson's disease. *Movement Disorders*, *31*(9), 1340–1340. https://doi.org/10.1002/mds.26682

Schwarz, D. S., & Blower, M. D. (2016). The endoplasmic reticulum: Structure, function and response to cellular signaling. *Cellular and Molecular Life Sciences*, *73*(1), 79–94. https://doi.org/10.1007/s00018-015-2052-6

Stoica, R., De Vos, K. J., Paillusson, S., Mueller, S., Sancho, R. M., Lau, K. F., Vizcay-Barrena, G., Lin, W. L., Xu, Y. F., Lewis, J., Dickson, D. W., Petrucelli, L., Mitchell, J. C., Shaw, C. E., & Miller, C. C. J. (2014). ER-mitochondria associations are regulated by the VAPB-PTPIP51 interaction and are disrupted by ALS/FTD-associated TDP-43. *Nature Communications*, *5*(1), 3996. https://doi.org/10.1038/ncomms4996

Stojanovski, D., Koutsopoulos, O. S., Okamoto, K., & Ryan, M. T. (2004). Levels of human Fis1 at the mitochondrial outer membrane regulate mitochondrial morphology. *Journal of Cell Science*, *117*(7), 1201–1210. https://doi.org/10.1242/jcs.01058

Szabadkai, G., Bianchi, K., Várnai, P., De Stefani, D., Wieckowski, M. R., Cavagna, D., Nagy, A. I., Balla, T., & Rizzuto, R. (2006). Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca^{2+} channels. *Journal of Cell Biology*, *175*(6), 901–911. https://doi.org/10.1083/jcb.200608073

Tatsukawa, H., & Hitomi, K. (2021). Role of transglutaminase 2 in cell death, survival, and fibrosis. *Cells*, *10*(7), 1842. https://doi.org/10.3390/cells10071842

Tilokani, L., Nagashima, S., Paupe, V., & Prudent, J. (2018). Mitochondrial dynamics: Overview of molecular mechanisms. *Essays in Biochemistry*, *62*(3), 341–360. https://doi.org/10.1042/EBC20170104

Toyofuku, T., Okamoto, Y., Ishikawa, T., Sasawatari, S., & Kumanogoh, A. (2020). LRRK2 Regulates endoplasmic reticulum-mitochondrial tethering through the PERK-mediated ubiquitination pathway. *The EMBO Journal*, *39*(2), e100875. https://doi.org/10.15252/embj.2018100875

Ugolino, J., Fang, S., Kubisch, C., & Monteiro, M. J. (2011). Mutant Atp13a2 proteins involved in parkinsonism are degraded by ER-associated degradation and sensitize cells to ER-stress induced cell death. *Human Molecular Genetics*, *20*(18), 3565–3577. https://doi.org/10.1093/hmg/ddr274

Vallese, F., Barazzuol, L., Maso, L., Brini, M., & Calì, T. (2020). ER-Mitochondria Calcium transfer, organelle contacts and neurodegenerative diseases. *Advances in Experimental Medicine and Biology*, *1131*, 719–746. https://doi.org/10.1007/978-3-030-12457-1_29

Vance, J. E. (1990). Phospholipid synthesis in a membrane fraction associated with mitochondria. *Journal of Biological Chemistry*, *265*(13), 7248–7256. https://doi.org/10.1016/S0021-9258(19)39106-9

Van Vliet, A. R., & Agostinis, P. (2018). Mitochondria-Associated membranes and ER stress. *Current Topics in Microbiology and Immunology*, *414*, 73–102. https://doi.org/10.1007/82_2017_2

Wang, X., Becker, K., Levine, N., Zhang, M., Lieberman, A. P., Moore, D. J., & Ma, J. (2019). Pathogenic alpha-synuclein aggregates preferentially bind to mitochondria and affect cellular respiration. *Acta Neuropathologica Communications*, *7*(1), 41. https://doi.org/10.1186/s40478-019-0696-4

Wider, C., Skipper, L., Solida, A., Brown, L., Farrer, M., Dickson, D., Wszolek, Z. K., & Vingerhoets, F. J. (2008). Autosomal dominant dopa-responsive parkinsonism in a multigenerational Swiss family. *Parkinsonism & Related Disorders*, *14*(6), 465–470. https://doi.org/10.1016/j.parkreldis.2007.11.013

Wilson, E. L., & Metzakopian, E. (2021). ER-mitochondria contact sites in neurodegeneration: Genetic screening approaches to investigate novel disease mechanisms. *Cell Death & Differentiation*, *28*(6), 1804–1821. https://doi.org/10.1038/s41418-020-00705-8

Wu, H., Carvalho, P., & Voeltz, G. K. (2018). Here, there, and everywhere: The importance of ER membrane contact sites. *Science (New York, N.Y.)*, *361*(6401). https://doi.org/10.1126/science.aan5835

Wu, S., Lu, Q., Wang, Q., Ding, Y., Ma, Z., Mao, X., Huang, K., Xie, Z., & Zou, M. H. (2017). Binding of FUN14 domain containing 1 with inositol 1,4,5-trisphosphate receptor in mitochondria-associated endoplasmic Reticulum membranes maintains mitochondrial dynamics and function in hearts in vivo. *Circulation*, *136*(23), 2248–2266. https://doi.org/10.1161/CIRCULATIONAHA.117.030235

Xu, L., Wang, X., & Tong, C. (2020). Endoplasmic Reticulum-mitochondria contact sites and neurodegeneration. *Frontiers in Cell and Developmental Biology*, *8*, 428. https://doi.org/10.3389/fcell.2020.00428

Yakhine-Diop, S. M. S., Rodríguez-Arribas, M., Canales-Cortés, S., Martínez-Chacón, G., Uribe-Carretero, E., Blanco-Benítez, M., Duque-González, G., Paredes-Barquero, M., Alegre-Cortés, E., Climent, V., Aiastui, A., López de Munain, A., Bravo-San Pedro, J. M., Niso-Santano, M., Fuentes, J. M., & González-Polo, R. A. (2021). The parkinsonian LRRK2 R1441G mutation shows macroautophagy-mitophagy dysregulation concomitant with endoplasmic reticulum stress. *Cell Biology and Toxicology*. https://doi.org/10.1007/s10565-021-09617-w

Yang, X., Li, Y., Zheng, L., He, X., Luo, Y., Huang, K., & Xu, W. (2019). Glucose-regulated protein 75 in foodborne disease models induces renal tubular necrosis. *Food and Chemical Toxicology*, *133*, 110720. https://doi.org/10.1016/j.fct.2019.110720

Yeo, H. K., Park, T. H., Kim, H. Y., Jang, H., Lee, J., Hwang, G. S., Ryu, S. E., Park, S. H., Song, H. K., Ban, H. S., Yoon, H.-J., & Lee, B. I. (2021). Phospholipid transfer function of PTPIP51 at mitochondria-associated ER membranes. *EMBO reports*, *22*(6), e51323. https://doi.org/10.15252/embr.202051323

Yoboue, E. D., Rimessi, A., Anelli, T., Pinton, P., & Sitia, R. (2017). Regulation of calcium fluxes by GPX8, a type-II transmembrane peroxidase enriched at the mitochondria-associated endoplasmic Reticulum membrane. *Antioxidants & Redox Signaling*, *27*(9), 583–595. https://doi.org/10.1089/ars.2016.6866

Youle, R. J., & Narendra, D. P. (2011). Mechanisms of mitophagy. *Nature Reviews Molecular Cell Biology*, *12*(1), 9–14. https://doi.org/10.1038/nrm3028

Zhang, L., Wang, J., Yang, B., He, Q., & Weng, Q. (2020). Role of DJ-1 in immune and inflammatory diseases. *Frontiers in Immunology*, *11*, 994. https://doi.org/10.3389/fimmu.2020.00994

Zhemkov, V., Ditlev, J. A., Lee, W. R., Wilson, M., Liou, J., Rosen, M. K., & Bezprozvanny, I. (2021). The role of Sigma 1 receptor in organization of endoplasmic reticulum signaling microdomains. *Elife*, *10*, https://doi.org/10.7554/eLife.65192

Zhu, Y., Wang, C., Yu, M., Cui, J., Liu, L., & Xu, Z. (2013). ULK1 And JNK are involved in mitophagy incurred by LRRK2 G2019S expression. *Protein & Cell*, *4*(9), 711–721. https://doi.org/10.1007/s13238-013-3910-3

Abbreviations

ER	endoplasmic reticulum
ATP	adenosine triphosphate
Ca^{2+}	calcium ion
OMM	outer mitochondrial membrane
IMM	inner mitochondrial membrane
PD	Parkinson’s disease
MERC	mitochondria-ER contact
IP_3R	inositol 1, 4, 5-triphosphate receptor
VDAC1	voltage-dependent anion channel 1
GRP75	glucose-related protein 75
MCU	mitochondrial calcium uniporter
α-syn	α-synuclein