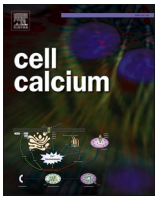
Cell Calcium 115 (2023) 102783

Contents lists available at ScienceDirect

Cell Calcium

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



Ca^{2+} signalling: A common language for organelles crosstalk in Parkinson's disease

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ARTICLE INFO

Keywords:
Calcium signalling
Mitochondria
Organelles contact sites
Parkinson's disease

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disease caused by multifactorial pathogenic mechanisms. Familial PD is linked with genetic mutations in genes whose products are either associated with mitochondrial function or endo-lysosomal pathways.

Of note, mitochondria are essential to sustain high energy demanding synaptic activity of neurons and alterations in mitochondrial Ca^{2+} signaling have been proposed as causal events for neurodegenerative process, although the mechanisms responsible for the selective loss of specific neuronal populations in the different neurodegenerative diseases is still not clear.

Here, we specifically discuss the importance of a correct mitochondrial communication with the other organelles occurring at regions where their membranes become in close contact. We discuss the nature and the role of contact sites that mitochondria establish with ER, lysosomes, and peroxisomes, and how PD related proteins participate in the regulation/dysregulation of the tethering complexes.

Unravelling molecular details of mitochondria tethering could contribute to identify specific therapeutic targets and develop new strategies to counteract the progression of the disease.

1. Introduction

Eukaryotic cell metabolism is strictly dependent on the compartmentalization of the intracellular pathways which are confined in membrane-bound organelles with specialized functions. However, intracellular organelles are not isolated entities but cooperate and reciprocally support their functions and activities by an active crosstalk and exchange of metabolites, ions and several second messengers [1,2]. Emerging data have demonstrated that the establishment of membrane contact sites (MCSs) represents a preferential way for inter-organelle communication. The close apposition between the membranes of two organelles in the absence of membranes fusion usually occurs in the range of 10–80 nm distance and creates a functional signalling hub [3]. MCSs occur between all the membrane-bound organelles and very interestingly they can also involve monolayer organelles, i.e., lipid droplets [4] and membraneless organelles, such as RNA [5] or stress granules [6].

MCSs are highly dynamic, thus allowing the quick and mutual adjustment in the transmission of signals among the coupled organelles [6–11]. Their formation is established by the interaction among a collection of tethering proteins and lipids that physically bridge the membranes in the juxtaposition regions [12,13]. A deep insight into the architecture of MCSs by functional and proteomics approaches has also unveiled the participation of non-tethering proteins which are in place to finely tune contacts maintenance and functions [7].

MCSs are involved in the regulation of different vital cellular homoeostatic processes ranging from lipid synthesis and metabolism, calcium (Ca^{2+}) and iron transfer, bioenergetics, cholesterol transport, organelles biogenesis and dynamics, autophagy etc. (Fig. 1).

Defective MCSs formation leads to impaired cell functions and has key implications for mechanisms underlying different diseases including several neurodegenerative disorders (NDs) [8–10] such as Alzheimer's disease [11], Parkinson's disease (PD) [12], and amyotrophic lateral sclerosis [13,14]. Interestingly, many of the proteins whose mutations are associated with familial forms of NDs have been shown to directly participate or interfere with MCSs formation [15–17].

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https://doi.org/10.1016/j.ceca.2023.102783
Received 13 June 2023; Received in revised form 25 July 2023; Accepted 26 July 2023
Available online 27 July 2023

In this respect, among all the interacting organelles, mitochondria are of special interest. Because of their relevance in cell bioenergetics and in the shaping of Ca^{2+} signals, they regulate many cellular pathways and cell fate [18,19]. Their correct functioning is particularly important for post-mitotic cells with high bioenergetic demands, such as neurons which require elevated ATP synthesis to sustain their synaptic activity [20]. The coordination of mitochondrial activities requires both a sophisticated organization in distinct mitochondrial sub-compartments and an intense communication with the other organelles. Thus, it becomes obvious that any dysfunction in such communication may preferentially affect neuronal cells and lead to neurodegenerative conditions [21,22].

The finding that mitochondria interact with nearly every other membrane-bound organelle in the cell and the constantly expanding identification of new functions for MCSs [23] justify the intense investigation on mitochondria contact sites in the perspective of clarify the molecular details at the basis of their interaction with the other organelles and identify new potential therapeutic targets or strategies to counteract the progression of the disease symptoms.

We have now understood that the number of contacts that mitochondria make with a specific organelle can vary dramatically from just a few to hundreds per cell and that they can occur at different distances and with different extents. It is now also well-accepted that not all the contacts are equal: structural differences due to the participation of different tethering proteins could selectively impact on the functional characteristics of the mitochondrial contacts and the dynamics of their formation.

Contacts between mitochondria and the endoplasmic reticulum (ER) have been firstly identified in the 1950s [24] and functionally appreciated as site for Ca^{2+} transfer in the 1990s [25].

Excitingly, over the past decades, contacts between mitochondria and vacuoles/lysosomes, peroxisomes, lipid droplets, endosomes, the Golgi apparatus, the plasma membrane, and nucleus [23,26,27] have been identified (Fig. 1) and the idea that many of them may share the common "Ca^{2+} language" to communicate is now very challenging.

The fact that multiple organelles simultaneously establish contact sites over time and that the formation of distinct contact sites could involve a different and selected pool of organelles further increased the spatial and temporal complexity of these interactions, opening new directions for investigation.

In this review, we will specifically discuss the literature regarding alterations of mitochondria tethering with other organelles in PD. We will focus our attention on the data available reporting a role of PD related proteins in the modulation of contact sites among mitochondria and three different organelles, ER, lysosomes, and peroxisomes, whose dysfunctions, in addition to the mitochondrial ones, have been described in different PD models and could be all linked with defective (mitochondrial) Ca^{2+} signalling.

2. Parkinson's disease: aetiology and mechanisms involved in the pathogenesis

PD is a devastating multifactorial ND characterized by the progressive loss of dopaminergic neurons (DA) in the substantia nigra pars compacta and the accumulation of intracellular inclusions within neurons and glia (mostly oligodendroglia), mainly composed of the presynaptic protein α-synuclein (αsyn) [28].

The observed progressive spreading in different areas of the brain of such inclusions, called Lewy bodies, suggested a way of diffusion/replication of αsyn oligomers in a prion-like manner according to the Braak's hypothesis [29–33], although the hypothesis itself is still controversial.

Globally, PD is considered the fastest-growing ND, with a worldwide incidence that ranges between 5–35 per 100,000 people/year and a prevalence that has doubled in the past 25 years and ranges between 100–300 new cases per 100,000 people. According to global statistics, approximately 1.5-2.0% of the ≥ 60 years population and 4% of people over 80 years of age are affected by PD [34].

PD is phenotypically characterized by either non-motor (e.g., cognitive impairment, autonomic dysfunction, disorders of sleep, depression and hyposmia) or severe motor symptoms (rigidity, bradykinesia, tremor, postural instability, and disability in functional performance) and therapies to counteract PD, principally based on pharmacological dopamine substitution or deep brain stimulation, offer only symptomatic relief without modifying the disease onset/progression [35]. Thus, a better understanding of the pathology and the development of new therapies are urgently needed.

Although most PD cases have sporadic aetiology, the 15% of PD have a familial history of the disease and nearly 10% are penetrant monogenic forms related to mutations or duplication in autosomal-dominant (*SNCA, PARK8*, and *VPS35*) and recessive (*PARK6, PARK7*, and *PRKN*) genes, see Table 1 [36–38]. So far, mutations in almost 20 genes were

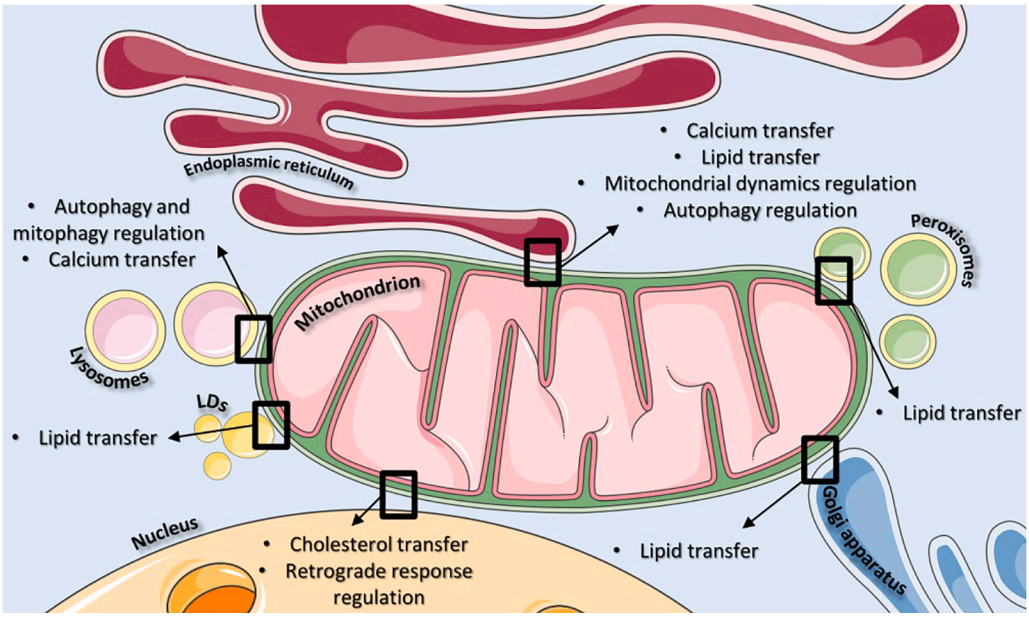

Fig. 1. Overview of the mitochondria contact sites with the other organelles. Mitochondria dynamically interact with almost every other organelle within cells by establishing contact sites with their membrane. The contact sites between mitochondria and endoplasmic reticulum, Golgi apparatus, nucleus, lysosomes, peroxisomes and lipid droplets are highlighted with black rectangular boxes. They represent an important hub where signalling molecules and ions are conveyed to regulate different processes, such as mitochondrial dynamics, mitophagy, autophagy and where the calcium and lipid transfer between the organelles occur. Of note, the contact sites between mitochondria and nucleus are involved in the regulation of the cell retrograde response induced by mitochondria dysfunction and contribute to the nuclear stabilization of prosurvival transcription factors by favouring cholesterol redistribution.

Table 1
Summary of genes predominantly associated with Parkinson's disease. Denomination and chromosomal location of PD genes are reported in the first column. Letter (c) indicates PD-causative genes and letter (s) indicates genes associated with susceptibility to PD, respectively. AD: autosomal dominant; AR: autosomal recessive. JO: juvenile onset (<21 years old); EO: early onset (21-50 years old), LO: late onset. sPD: sporadic PD. *, UCH-L1 role in PD is still uncertain [196].

PD gene	Inheritance	Function	Variants *frequency of mutations*	Form of PD	Year of discovery Ref
SNCA (c) 4q21-22	AD *Risk factor*	Regulation of synaptic vesicle trafficking and neurotransmitter release	Point mutations (A30P,E46K,A53T) duplication, triplication *Rare (0.5-2% of adult PD)*	Parkinsonism with common dementia	1997 [28, 197]
LRRK2 (c) 12q12	AD *Risk factor*	Kinase and GTPase activity, cytoskeletal dynamics, protein translation	>40 point mutations (7 are pathogenic, including the common G2019S) *Up to 10% in fPD; 3% in sPD; up to 30% in several ethnic populations*	LO	2004 [198, 199]
VPS35 (c) 16q11.2	AD	Component of retromer complex	>5 point mutations *Rare (0.3% in fPD; 1% in sPD)*	LO	2011 [200, 201]
UCH-L1 * 4p13	AD	Ubiquitin carboxyl-terminal hydrolase	I93M point mutation *Very rare (less than 1% PD cases)*	LO	1999 [202]
DJ-1 (c) 1p36.23	AR	Redox sensitive molecular chaperone	>10 point mutations and large deletions *Rare (up to 1%-2%)*	EO	2003 [107]
Parkin (c) 6q26	AR *Risk factor*	Ubiquitin ligase- targeted to mitochondria to aid mitophagy	>100 point mutations, exonic rearrangements *4.6%-10.5% of EO PD*	JO,EO	1998 [48]
PINK1 (c) 1p36.12	AR	Protein kinase - required for parkin-mediated mitophagy	>40 point mutations, rare large deletions *Up to 8% of PD cases*	EO	2004 [49]
ATP13A2(c) 1p36.13	AR	Lysosomal P-ATPase	>5 point mutations *Very rare (a total of 30 patients)*	Kufor-Rakeb syndrome (KRS) or JO atypical PD, EO	2006 [59]
DNAJC6 (c) 1p31.3	AR	Endosomal function/Chaperone activity	>5 point mutations, deletion *Rare (less than 1% PD cases)*	JO, EO	2012 [203]
PLA2G6 (c) 22q13.1	AR	Phospholipase	>10 point mutations *Very rare (less than 1% or even rarer)*	EO dystonia-parkinsonism	2009 [204]
FBXO7 (c) 22q12.3	AR	f-box protein phosphorylation dependent ubiquitination	2 point mutations *Very rare (less than 1%)*	EO atypical parkinsonism related syndromes	2008 [205, 206]
GBA (s) 1q22	AR *Most common risk factor*	Glucocerebrosidase active in lysosomes	>300 point mutations *5-15% of adult PD, this percentage can vary widely depending on the specific population, ethnic group and geographic region being analyzed*	LO, EO	2003 [61]

found to be related to PD and genome-wide association studies, conducted to identify genetic factors contributing to PD, allowed to recognise 19 PD -causing genes, thus suggesting that a percentage of the so-called idiopathic PD could be inherited [39,40]. Among these, an important risk factor related to PD is the monoallelic mutation of the *GBA1* gene (encoding for the lysosomal glucocerebrosidase enzyme) [41], that also represents the causative gene for Gaucher's disease, a lysosomal storage disorder characterized by the accumulation of glycosphingolipids [42]. At the cellular level, multiple affected processes were identified in PD, including altered proteostasis, ER stress, Ca^{2+} dyshomeostasis, defective axonal transport, neuroinflammation, traffic vesicles impairment, mitochondrial and lysosomal dysfunctions [43, 44]. The study of familial forms of PD and the identification of proteins encoded by genes associated with PD have greatly contributed to define molecular pathways that, when altered, can trigger PD neurodegeneration. Some of these proteins are clearly implicated in the mitochondria quality control pathways [45], and have been shown to interfere with the general process of autophagy [46], that aims at degrading long-lived proteins and dysfunctional or superfluous organelles in eukaryotic cells.

Mutations in the *PARK6* and *PRKN* genes, encoding *PINK1* and Parkin proteins respectively, are responsible of approximately one-half of the genetically linked early onset PD cases [47–49] and have been directly related to the impairment of mitophagy, the quality control process crucial to selectively eliminate damaged mitochondria [50–53]. Mitochondrial impairment is also associated to mutations in other PD-related genes, such as *PARK8* encoding *LRKK2, PARK7* encoding DJ-1, *ATP13A2* encoding the relative ATPase and *SCNA* encoding αsyn [54–59].

Other mutations, including those in *GBA1* and *PARK8* genes, have an impact not only on mitochondrial functions but also on lysosomes maintenance, thus suggesting that perturbation of lysosomes-related activities may contribute to PD pathogenesis [41,60,61].

3. Mitochondria dysfunctions in sporadic and genetic PD forms

Although the pathogenesis of PD is undoubtedly multifactorial, several lines of evidence suggest that mitochondria impairment triggers the onset and progression of the disease, in both familial and idiopathic cases [62,63].

The first observation suggesting that mitochondrial dysfunctions play a potential role in sporadic PD came in the 80′s by observing that degeneration of DA neurons in seven patients affected by parkinsonism was related to the consumption of synthetic heroin containing 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a by-product of the synthesis of 1-methyl-4-phenyl-4-propionoxypiperidine [64–67]. Later, it has been demonstrated that, after crossing the blood brain barrier, MPTP is selectively imported in DA neurons and converted into MPP+ by the monoamino oxidase, where it accumulates into the mitochondria and inhibits mitochondrial complex I (MCI) and the electron transport, causing a reduction of ATP and the increase of reactive oxygen species (ROS) [66,68,69]. Degeneration of DA neurons is also caused by other pesticides, such as paraquat and rotenone, both acting as respiratory chain complexes inhibitors [66,70,71], thus confirming the close relationship between the maintenance of mitochondrial functionalities and PD onset and progression.

Interestingly, deficiency of MCI and impaired electron transport represent hallmarks of sporadic and genetic forms of PD [72–76]. Defects in other mitochondrial complexes (II, III and IV) were also found in post-mortem tissues of PD patients [77–79]. The connection between defects in oxidative phosphorylation and PD pathogenesis was recently reinforced by a paper which reported that the ablation of the Ndufs2 subunit of MCI complex in DA neurons, in conditional Ndufs2-KO mice, caused a Warburg metabolic shift which first caused a progressive axonal loss of function and, later, an overall DA neurons loss in the *substantia nigra*, resulting in a levodopa-responsive parkinsonism [80].

As mentioned above, proteins implicated in familial forms of PD are closely involved in the maintenance of a healthy pool of mitochondria

and their loss or gain of functions profoundly impact mitochondria through different mechanisms. We will briefly mention them to have a general overview, but we invite the readers to refer to the wide literature for more details [21].

αsyn is a small cytosolic protein which plays an important role in synaptic transmission and its PD-related mutants or aggregated forms have been associated to mitochondrial dysfunction [63,81,82]. Indeed, excessive accumulation and oligomerization of αsyn are responsible for impaired MCI activity [83], mitophagy [84], mitochondrial protein import defects [85] and perturbation of mitochondrial Ca^{2+} uptake [86]. Different reports indicated that monomeric and oligomeric αsyn forms differently interact with the mitochondrial ATP synthase, the former acting as a positive physiological regulator and promoting ATP synthesis [87] and the latter as a pathological toxic gain of function species which induces oxidation of ATP synthase, ROS production and mitochondrial membranes damage by the opening of the permeability transition pore (PTP)[88,89]. Others have shown that the overexpression of αsyn is sufficient to induce mitochondrial fragmentation [90] and impaired macroautophagy via Rab1a inhibition [91].

LRRK2 is a leucine-rich repeat kinase and the mutations associated with familial forms of PD increase its kinase activity and its association to microtubule [92–95]. Mitochondrial dysfunctions ranging from mtDNA damages [96], loss of mitochondrial membrane potential, and decreased complex IV activity and ATP levels were found in patient-derived cells [57,97]. Interestingly, perturbation of Ca^{2+} homeostasis has been also reported: patient fibroblasts and cortical neurons expressing mutant LRRK2 showed higher levels of the mitochondrial Ca^{2+} uniporter MCU and its positive regulator MICU1, resulting in mitochondrial Ca^{2+} overload and dendric injuries [98]. Others have shown that LRRK2 deletion and mutations led to an impaired mitochondrial Ca^{2+} extrusion via $Na^{+}/Ca^{2+}/Li^{+}$ exchanger (NCLX) which, in turn, lowered the PTP opening threshold and increased cell death [99].

MCI deficiencies [100], altered mitochondrial morphology, a defective autophagic pathway and accumulation of damaged mitochondria [101] were also found in MEF cells from transgenic mice expressing a PD-related mutant LRRK2.

As for *PINK1* and Parkin, they are both engaged in the clearance of damaged mitochondria by mitophagy [102]. PINK1 is a mitochondrial serine/threonine protein kinase and is required for the recruitment of parkin, a cytosolic E3 ubiquitin ligase, at the outer mitochondrial membrane upon mitochondria damage, and the triggering of stress-induced mitophagy. Thus, it is obvious that perturbation of such process could be strictly associated to mitochondrial impairment, even if less evident is the specific association with PD pathogenesis [50–53,103,104]. Thus, much more investigations are needed to unveil the involvement of mitochondrial dysfunctions in PD.

In addition to their role in mitophagy, PINK1 and parkin have been described to influence mitochondrial Ca^{2+} handling. Seminal work by Marongiu et al. gave the first indication that mutant PINK1 could interfere with mitochondrial Ca^{2+} fluxes [105]. Later, it has been proposed that PINK1 regulates Ca^{2+} efflux from mitochondria via NCLX: Gandhi et al. proved that PINK1 deficiency results in mitochondrial Ca^{2+} overload and subsequent ROS production. Furthermore, mitochondria isolated from the brains of mice lacking PINK1 seem to be more vulnerable to cell death [106].

PARK7 gene encodes the multifunctional DJ-1 protein, whose mutations are linked with autosomal recessive familial Parkinson's disease [107]. It prevalently localises in the cytoplasm but has been found also in the nucleus and in the mitochondria, both at the level of the outer mitochondria membrane and the matrix [108]. DJ-1 loss of function is related to increased susceptibility to oxidant stress [109] and neuronal cell death, implying a neuroprotective role for the protein [110,111]. Endogenous DJ-1 acts not only as a redox sensor and ROS scavenger, but also as a molecular chaperone and transcriptional regulator. Moreover, DJ-1 plays a crucial role in maintaining the integrity and function of the mitochondrial network, and in the control of mitochondrial Ca^{2+} homeostasis by regulating ER–mitochondria functional interactions (see below). However, there are only little evidence suggesting a direct role in mitochondrial function. An impairment in the assembly and activity of complex I have been observed in DJ-1 null mouse derived dopaminergic cells [112,113]. In line with this, we have shown that DJ-1 overexpression enhanced ATP production, promoting mitochondrial elongation and respiratory chain super-complexes assembly [114].

Finally, as already mentioned, mitochondrial dysfunction is also a feature of *GBA1*-related PD cases [41,61,115]. Indeed, human DA cell lines [116], as well as neuronal and glial cells obtained from transgenic mice harbouring *GBA1* mutations [117,118] and neurons differentiated from *GBA1*-PD patients [119] display mitochondrial fragmentation, reduced respiratory chain complex activities, decreased mitochondrial membrane potential (MMP) and lower oxygen consumption, as well as defects in mitochondrial morphology and energy metabolism. Intriguingly, Baden and co-workers recently demonstrated that the *GBA1* encoded protein glucosyl ceramidase (GCase) is imported into the mitochondria where it promotes the maintenance of MCI integrity and function, participating in its quality control process [120]. Accordingly, downregulation of mitochondrial fusion proteins and impaired mitophagy machinery were also found in post-mortem tissues derived from PD patients bearing *GBA1* mutations [121].

The evidence mentioned above are only a fraction of all the information available in the literature about mitochondria dysfunctions shared among the different PD forms. Also, it is now clearly emerging that the connection between mitochondria and the other organelles might be tightened or loosed, affecting not only mitochondrial, but also the other interacting organelle's functions.

4. Could altered mitochondrial contacts be a common feature in PD pathogenesis?

DA neurons of substantia nigra pars compacta are autonomous pacemakers, thanks to the activity of plasma membrane Cav1.3 L-type Ca^{2+} channels that provide membrane depolarization and spiking in the absence of synaptic input [122]. Their activity is necessary to sustain dopamine release to striatal neurons and to guarantee high energy demands that are required for this function. Recently it has been shown that the close coupling of the plasma membrane Cav1 Ca^{2+} channels with the Ca^{2+} release channels of the ER, i.e., the ryanodine receptors (RyRs), represents the main route to activate the tricarboxylic acid cycle (TCA) and increase ATP production in DA neurons [123]. In this way RyRs-dependent Ca^{2+} release functionally couples plasma membrane Cav1 channels to mitochondria which, similarly to what has been described in cardiac cells [124], are docked to the ER at MAMs.

If continuous Ca^{2+} entry sustains dopamine secretion and mitochondrial metabolism, at the same time exposes mitochondria to "Ca^{2+} and oxidant stress", due to continuous stimulation of the electron transfer chain also in the absence of bioenergetic demands. In animal models, the administration of L-type channels blocker isradipine has been proven to reduce mitochondria damage [125]. However, continuous Ca^{2+} entry may also synergize with mutations in PD-related proteins that impact on ER-mitochondria contact sites and contribute to exacerbate mitochondria damage and cell degeneration. Thus, the deep understanding of the molecular determinants involved in the regulation of ER-mitochondria tethering became crucial to the identification of new potential disease-modifying targets and the development of new strategies to tackle compromised mitochondria function and subsequent bioenergetic impairments that contribute to the loss of dopaminergic neurons in PD.

As previously mentioned, in the last decade an increasing amount of data reported impaired communication between mitochondria and ER in many cellular and animal models of PD, and the possibility that alterations in this specific inter-organelles crosstalk may represent a PD-related pathogenic mechanism is now widely recognized. More

recently, the idea that the communication between mitochondria and other contacting organelles could be compromised in PD has consistently emerged, and intriguingly it has been proposed that it could share the common language of Ca^{2+} signal.

Mitochondria contacts with other organelles and the interference of PD-related proteins in these relationships are discussed in this review.

4.1. A brief overview of ER-MT contacts tethering complexes

A mutual relationship between ER and mitochondria (MT) is crucial for the maintenance of cellular lipid and Ca^{2+} homeostasis, mitochondria metabolism, as well as many other intracellular processes and signaling pathways [25,126–129]. Such a relationship is allowed by the formation of highly dynamic ER-MT contact sites at the Mitochondria-Associated Membranes (MAMs) that contribute to the formation of specific microenvironments where the communication between the two organelles becomes very tight.

Even though the focus of this review is not on ER-MT crosstalk, the main actors at this organelle interface are here briefly described to provide some context for understanding how ER-MT contact sites modulation could be linked to PD. The tethering between the ER and mitochondrial membranes has been extensively investigated and many different protein complexes responsible for their physical association have been identified during the last decades. We report here below the most characterized ones, being conscious that the list is not exhaustive and other partners are still being discovered. Fig. 2 refers to protein complexes that have been shown to be modulated by PD related proteins.

The best known of these complexes is the tripartite complex consisting of the ER Ca^{2+}-release channel IP3R (inositol-1,4,5-trisphosphate receptor), the voltage-gated anion channel 1 (VDAC1), situated in the outer mitochondrial membrane (OMM), and the cytoplasmic chaperone glucose-regulated Protein 75 (Grp75). By favouring the close apposition between ER and mitochondria membrane, the two channels form a preferential route for Ca^{2+} transfer from ER to mitochondria: Ca^{2+} ions released by the opening of IP3Rs are transferred to the mitochondrial intermembrane space via VDAC1, thus generating microdomains with high Ca^{2+} concentration that relieve the gatekeeping control by MICU1-MICU2 regulatory subunits on the low affinity, high capacity mitochondrial Ca^{2+} uniporter pore subunit (MCU) of the inner mitochondrial membrane and activate Ca^{2+} ions transport in the mitochondrial matrix. GRP75 acts as a scaffold protein for the IP3R–VDAC complex, allowing a structural and functional coupling between the IP3-sensitive ER Ca^{2+} stores and mitochondria [130–132], thus contributing to create a platform for Ca^{2+} microdomains generation.

Another complex widely recognized comprises the vesicle-associated membrane protein B (VAPB), an ER-resident protein, and the protein tyrosine phosphatase-interacting protein-51 (PTPIP51) located at the OMM [14,133]. Interestingly, also the tethering between VABP and PTPIP51 participates in the IP3R-mediated delivery of Ca^{2+} to mitochondria and in autophagy synaptic activity [134,135]. The profusion protein Mitofusin 2 (Mfn2), which is expressed on the outer mitochondria membrane, is a GTPase protein known to facilitate ER-MT tethering by forming trans-organelle hetero- or homo-dimer tethers [136,137]. Its precise role in maintaining ER-MT tethering has been widely discussed in the past years and it has been proposed to act both as a linker and a spacer [138,139]. The list of MAMs protein complexes also includes the mitochondrial fission protein 1 (Fis1) and the ER-resident protein B-cell receptor-associated protein 31 (BAP31) [140], as well as Synaptojanin-2-binding protein (SYNJ2BP), the ribosome-binding protein 1 (RRBP1) [141,142], or FK506-binding protein, 8 (FKBP8) [143], VAP-interacting protein vacuolar protein sorting-associated protein 13 A (VPS13A) [144–146], PDZ domain containing 8 (PDZD8) [147] and the complex Spire 1C-Inverted formin 2 (INF2) [148].

4.2. Alterations of ER-MT contacts in PD

In the last decades, PD has been associated to a plethora of deregulated cellular processes, involving, among others, Ca^{2+} homeostasis, oxidative balance, mitochondrial activity, and the autophagic flux. Since ER-MT communication has been linked to the regulation of many of these cellular processes and since many PD-related proteins have been found enriched at MAMs, ER-MT interactions have been extensively investigated focusing on the functions of PD related proteins.

Here we report the major findings on PD related proteins pathogenic mutations impact on ER-MT tethering (see Fig. 2).

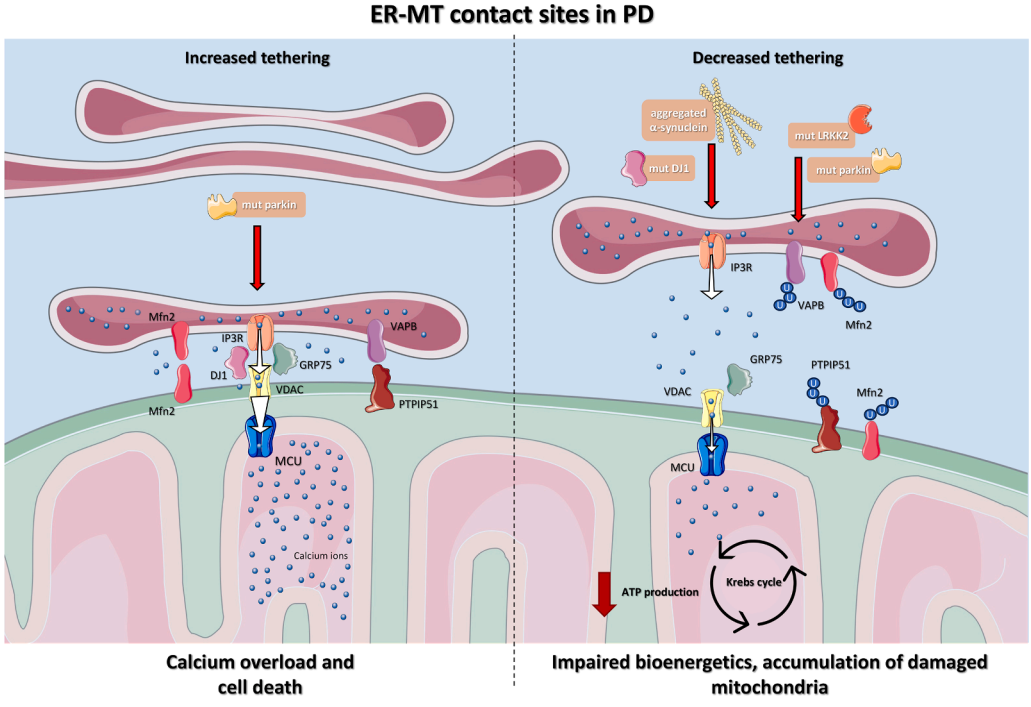

Fig. 2. The endoplasmic reticulum (ER) – mitochondria (MT) contact site in Parkinson's disease (PD). The major protein complexes involved in tethering ER-MT membranes and their modulation by PD-related proteins are shown in this cartoon. Mfn2, VAPB-PTPIP51 and IP3R-GFRP75-VDAC are engaged to keep ER-MT in close contact and favour ER to MT Ca^{2+} transfer to sustain Krebs cycle and ATP production. The panel on the right shows that PD-related mutant proteins reduce ER-MT contact sites formation by interfering with VAPB-PTPIP51 and IP3R-GFRP75-VDAC tethering complex and thus lead to bioenergetics impairment and accumulation of damaged mitochondria. In the left panel: parkin mutants have also been shown to enhance ER-MT contact sites formation, resulting in mitochondrial calcium overload, opening of the mitochondrial permeability transition pore (mPTP) and cell death.

4.2.1. SNCA

Despite the central role of αsyn in PD pathology, its physiological function, and its involvement in the development of the disease are still partially unclear. Regarding ER-MT contacts, our group revealed the participation of αsyn in contact sites formation and demonstrated that moderated αsyn overexpression in Hela and in SHSY5Y cells increased the ER-MT tethering and positively enhanced mitochondrial Ca^{2+} transients generated upon Ca^{2+} release from the ER, thus sustaining bioenergetic metabolism. However, when the overexpression is exaggerated and caused the redistribution of cytosolic αsyn to foci this positive modulation is lost [86,149]. Later, the presence of αsyn at MAMs, where it interacts with the chaperone Grp75, has been confirmed [150, 151], reinforcing its direct involvement in the physiological regulation of ER-MT communication. Since then, different reports suggested that αsyn abundance could compromise the ER-MT tethering in different ways, thus making the precise role of αsyn at this organelle interface apparently controversial. Indeed, Paillusson et al. showed that αsyn overexpressing SH-SY5Y cells and dopaminergic neurons derived from iPS cells of a *SNCA* triplication patient, displayed a reduction in the formation of the VAPB-PTPIP51 tethering complex, with a consequent decrease in ER-MT juxtaposition, mitochondrial $Ca2^{+}$ flux, and ATP production [152]. In HEK293 cells, upon overexpression of the WT or mutant form of the protein, Erustes et al. reported a reduction in the contact sites between the two organelles due to a decreased IP3R–GRP75 interaction [153]. These results appear in contrast; however, they could be nicely rationalized by the existence of a dose dependent mechanism for αsyn action on ER-MT contact sites. At a low level of expression and presumably in a monomeric form, αsyn acts as a tether between ER and mitochondria, thus sustaining ATP production. Instead, under strong overexpression αsyn redistributes to cytosolic foci where presumably aggregates, thus losing its ability to modulate ER-MT contact site formation and leading to impaired bioenergetics and mitochondria damage according to a loss of function mechanism (Fig. 2). In agreement with this view, the results obtained recently by Ramezani et al. reinforced the evidence that αsyn can participate as a tethering protein to modulate Ca^{2+} flux between ER and mitochondria in physiological conditions. Furthermore, they have found that αsyn phosphorylation and aggregation caused by toxins that induce mitochondrial stress prevented cellular recovery from mitochondrial Ca^{2+} overload, thus indicating a pathological role for αsyn under these conditions [154].

4.2.2. DJ-1

In 2013, we reported that DJ-1 was present at the MAMs fraction in mice brain and that its overexpression in HeLa cells caused an increase in the juxtaposition between ER and mitochondria membranes, which in turn was responsible for increased mitochondrial Ca^{2+} uptake upon cell stimulation (Fig. 2). In line with this, DJ-1 silencing resulted in reduced ER-MT tethering [155]. Later, DJ-1 was identified as a critical component of the multicomplex containing IP3R3-Grp75-VDAC1 at MAMs, further reinforcing the role of the protein in the maintenance of this organelle connection [156]. In this respect, the loss of the protein decreased ER-MT contacts both in DJ-1 KO dopaminergic cell lines and in neurons in the substantia nigra of DJ-1 KO mice [156] and the reintroduction of pathogenic DJ-1 mutants was not able to rescue the phenotypes suggesting that impaired ER-MT association could contribute to the pathogenesis of PD. Interestingly, it has also been shown that DJ-1 deficiency aggravates αsyn aggregation by inhibiting the activation of autophagy [157], thus providing a link between PD-related proteins, autophagy, ER-MT tethering and bioenergetics.

4.2.3. PINK1/Parkin

In addition to their well-established role in the mechanism of mitophagy, PINK1 and Parkin have been also linked to the modulation of MAMs, although further investigations are needed to better understand their involvement in the ER-MT communication. Their presence at the ER-MT interface has been confirmed both in basal conditions and following mitophagic stimuli. It has been shown that the CCCP treatment of neuroblastoma SHSY5Y cells strongly redistributed PINK1 protein at MAMs together with Beclin1, a pro-autophagic protein, inducing an increase in ER-MT juxtaposition and regulating the nucleation of the omegasomes (the precursors of autophagosomes) [158]. Moreover, the silencing of PINK1 in M17 dopaminergic cells caused a reduction in the number of ER–mitochondria contact sites and an increase in their distance [159], suggesting a crucial role of PINK1 in their regulation, even in the absence of mitochondrial damage and, thus, independently from the activation of the mitophagy response.

The participation of Parkin in the ER-MT contact sites formation is more controversial (Fig. 2). Upon overexpression in Hela cells and SHSY5Y cells, Parkin enhanced ER-MT tethering which correlated with an increase in mitochondrial Ca^{2+} uptake and ATP production [160], suggesting its participation in sustaining the mitochondrial bioenergetics. In agreement with this finding, Basso et al. reported that in Parkin deficient cells and parkin mutant human fibroblasts the tethering between ER and mitochondria is decreased [161], and proposed a role for Parkin-mediated ubiquitination of Mfn2 in the maintenance of ER-MT contact sites. Different results have been obtained by others analysing primary cells from patients with PARK2 mutations and from PARK2 KO mice where the ER-MT juxtaposition was found to be increased compared to controls [162]. Data obtained in Drosophila have demonstrated that the increase in ER stress observed in parkin mutant flies correlates with increased coupling between ER and defective mitochondria in a mitofusin-dependent manner and that, under condition of mitochondrial damage, a reduction of ER-MT contact sites could be neuroprotective [163]. These results underline the fact that the quality of contact sites rather than the quantity makes the differences: the balance between the contacts that are in place to sustain bioenergetics and those that impact on ER stress is crucial and may explain discrepancies found in the different PD models.

In addition to this, PINK1 and Parkin indirectly affect ER-MT communication during mitophagy, as some of their targets are involved in the regulation of these organelles' interaction. For example, besides the phosphoubiquitination of Mfn2 mediated by PINK1/Parkin [164], parkin ubiquitinates MITOL, a mitochondrial ubiquitin ligase, leading to its translocation to peroxisomes [165]. Since MITOL regulates ER-MT contacts via Mfn2, its delocalization might be a way to indirectly affect the juxtaposition between the two organelles. Another target of PINK1 and Parkin is the Rho GTPase 1 (Miro1), which, apart from its role in the mitochondria transport machinery, is also involved in the crosstalk between ER and mitochondria [166]. By targeting Miro1 to degradation, PINK1/Parkin might influence ER-MT tethering. As for Miro1, moreover, it is worth mentioning that two heterozygous mutations in the Miro1 encoding gene RHOT1 have been identified in two PD patients, and that ER-MT contacts are decreased in fibroblasts derived from these patients [167], further reinforcing the connection among ER-MT communication and PD.

4.2.4. LRRK2

Recently, the kinase activity of the leucine-rich repeat kinase 2 (LRRK2) has been directly linked to the modelling of ER-MT crosstalk via the regulation of the E3 ubiquitin ligases MARCH5, MULAN, and Parkin. The enhanced kinase-activity of the pathogenic LRRK2(G2019S) mutant caused the dissociation of these ligases from LRRK2, leading to their PERK-mediated phosphorylation and activation, which resulted in promoting ubiquitin-mediated degradation of ER-MT tethering proteins (Fig. 2). CRISPR/Cas9 engineered MEFs cells expressing the PD-related LRRK2 G2019S mutant have lower level of Mfn1, Mfn2 and Fis1 as well as reduced ER-to-mitochondria Ca^{2+} transfer and oxidative phosphorylation rate. Accordingly, ER-MT contact sites were decreased, implying a role of LRRK2 in the modulation of the interface between these two organelles and of the mitochondrial bioenergetics [168]. By contrast, the kinase-dead LRRK2(D1994A) mutant blocked PERK-mediated

phosphorylation and activation of E3 ligases, thereby increasing the levels of ER-MT tethering proteins. Thus, the kinase activity of LRRK2 represents an important control point for ER-MT interaction and, in turn, cell fate [168].

4.2.5. CRELD1

The link between defective ER-MT cross-talk and PD pathogenesis has been further strengthened by a recent study by Paradis et al. They have found that the poorly characterized CRELD1 risk gene for PD encoded for a protein, the ER cysteine-rich with EGF-like domain (CRELD1), which is implicated in the regulation of the ER stress response and is localized at ER-MT contacts. The loss of function of this protein resulted in a decrease in the organelles juxtaposition. Interestingly, Drosophila CRELD1 mutants exhibited a strong PD-like locomotion deficit, mitochondrial hyperfusion, and complex I deficits with aberrant ROS signaling which possibly affected dopaminergic neurons activity [169].

4.3. Alterations of lysosomes-mitochondria contacts in PD

Lysosomes-mitochondria (LY-MT) contacts have become increasingly appreciated key players in neuronal biology and are widely spread in the soma, axons, and dendrites of neurons. Such contacts are principally devoted to the transfer of Ca^{2+}, iron and cholesterol between the two organelles and have a functional significance independent from the degradative pathway's activation (i.e., mitophagy) or from the formation of mitochondria-derived vesicles. Pioneering studies by the Krainc's group have established that LY-MT contacts facilitated the direct transfer of Ca^{2+} from lysosome to mitochondria through the Mucolipin-1 (TRPML1) lysosomal channel [170]. The master regulator of such interaction is the small GTPase Rab7. Briefly, while GTP-bound Rab7 favours contacts formation, GTP hydrolysis shifts the balance to the untethering of the two organelles [171,172]. Such hydrolysis is favoured by TBC1D15, a GTPase activating protein (GAP) localized at the OMM, thanks to its binding to Fis1 protein [173]. Other known LY-MT tethering proteins are represented by GDAP1, a glutathione S-transferase linked to the outer mitochondrial membrane, that interacts with the lysosomal membrane protein LAMP1 [174] and Mfn2, whose down-regulation was shown to increase the distance between the two organelles in primary human erythroid progenitors [175]. Fig. 3A summarizes the mechanism for LY-MT contact sites formation.

As mentioned above, one of the most important genetic risk factors for PD is the loss-of-function mutation of *GBA1*. The consequent decreased GCase activity causes lysosomal accumulation of glycosylceramide which is one of the hallmarks of Gaucher's disease and, interestingly, was also found in many familial and sporadic forms of PD [176]. More recently, Krainc and co-workers have shown that GBA1-mutated DA neurons derived from PD patients are characterized by a reduced expression of TBC1D15, which resulted in defective LY-MT contact untethering and prolonged duration of LY-MT contacts, ultimately affecting mitochondrial distribution and function [177].

Since the GCase activity was found to be reduced in both idiopathic and familial PD patient derived neurons [119,178], the possibility that targeting GBA1 or TBC1D15 expression level may represent a potential disease-modifying therapy for PD has been proposed.

This perspective is further supported by the recent finding that also Parkin is involved in the maintenance of proper balance between tethering and untethering events of LY-MT contacts by stabilizing GTP-bound Rab7 at lysosome membrane and favouring their formation. Intriguingly, LY-MT contacts were reduced in parkin PD patient iPSC-derived dopaminergic neurons, resulting in a deficiency of amino acids levels in mitochondria and accumulation in lysosomes, suggesting that LY-MT contacts are the site for interorganellar amino acids transfer [179]

Interestingly, it was also demonstrated that PINK1 participates to the formation of endosome-mitochondria contacts during the process of extracellular vesicles formation, allowing dissemination of pro-invasive microenvironments during mammary carcinoma progression [180]. In this way, PINK1 regulates the transfer of mtDNA to recipient cells and it is possible that PINK1 loss of function in PD could also impact on LY-MT contacts. Further studies are necessary to explore these aspects and the role of PD-related proteins in the dynamics of tethering and untethering processes that regulate the abundance and the duration of LY-MT contact sites in addition to the best well characterized ER-MT contact sites.

4.4. Alterations of peroxisomes-mitochondria contacts in PD

Peroxisomes (PO) cooperate and communicate with mitochondria to maintain cellular pathways such as fatty acid β-oxidation, amino acid catabolism, ROS detoxification, and clearance of defective organelles [181–183]. The connection between POs and mitochondria is very tight: the two organelles share transcriptional regulatory mechanisms that allow them to coordinate their relative abundance and their enzyme content, including division machinery key proteins [184].

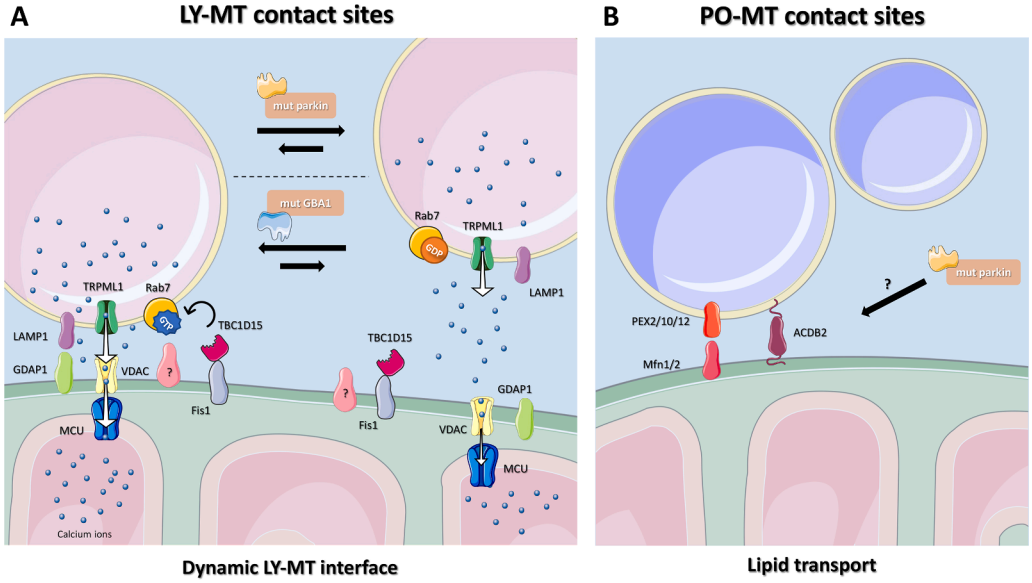

Fig. 3. Mitochondria interactions with lysosomes (A) and peroxisomes (B) and the involvement of PD-related proteins. Panel A, Contact sites between mitochondria (MT) and lysosomes (LY) are maintained by LAMP1 and GDAP1 tethering complex and dynamically regulated by Rab7/TBC1D15 (see the text). PD-related GBA1 mutant affects TBC1D15 activity and prolonged the duration of LY-MT contact sites. Otherwise, PD-related parkin mutant impinges Rab7 stability, thus reducing LY-MT contacts. Panel B, Contact sites between MT and peroxisomes (PO) are formed by the interaction of Mfn1/2 with PEX2, PEX10 and PEX12, and by the splice variant 2 of ACBD protein. No direct evidence for specific action of PD-related proteins in their regulation has been provided so far but a possible role for parkin through Miro1 ubiquitination has been proposed (see the text).

Different mechanisms have been proposed to participate in PO-MT communication, such as diffusion, vesicular transport, and membrane tethering [181,185,186] but molecular details are still elusive. Up to now, the most widely recognized PO-MT tethering complex in mammalian cells consists in the splice variant of enoyl-CoA δ isomerase 2 (ACBD2/ECI2A), containing both a N-terminal mitochondrial targeting signal and a C-terminal peroxisomal targeting signal [187]. Recently, it has been proposed that Mfn1 and 2 could participate to PO-MT contacts formation through their interaction with the peroxisome transmembrane PEX2, PEX10 and PEX12 proteins [188]. See Fig. 3B for a representative cartoon.

Accumulating evidence points out the importance of PO and mitochondrial dysfunction in aging as well as in many neurodegenerative diseases [189,190]. Nowadays, there are only indirect data regarding a possible correlation between PO-MT tethering dysfunctionalities and PD pathogenesis. it has been reported that the abnormal accumulations of αsyn in the brain correlates with perturbations in both PO biogenesis [191] and pexophagy [191–193]. However, it is not known whether defects in PO metabolism and biogenesis could be due to a defect in their communication with mitochondria. The upregulation of Rho GTPase Miro1 observed in PD patients [194] could suggest an outcome on PO-MT communication, since the Miro1 yeast orthologue, Gem, is an important regulator of PO-MT contacts [186]. Moreover, it was shown that Miro1 and its peroxisome-enriched splice variant could participate in connecting ER to mitochondria and peroxisomes by recruiting the lipid transport VPS13D protein [195]. Considering that Miro1 is a parkin substrate, parkin loss of function could contribute to PD pathogenesis not only by impacting on the mitophagy pathway or the formation of ER-MT contact sites as mentioned above, but also by perturbing PO-MT communication. Further investigations are needed to provide more information regarding the role of VPS13 in organelles tethering and its implication in the mechanism of PD onset and progression.

5. Conclusions

Mitochondrial dysfunction is a hallmark associated with the progression of many neurodegenerative diseases and it has been suggested that it may also contribute to their pathogenesis.

Many studies have highlighted a possible link between mitochondrial dysfunction and the dysregulation of the inter-organelle crosstalk, proposing that interventions devoted to preserve the correct signalling at MCS could represent new therapeutic strategies. This aspect is particularly relevant in the case of PD since in many different cellular and animal models it has been observed that PD-related proteins participate to the regulation of the number, extension and duration of ER-MT and LY-MT contact sites by directly interfering with the tethering protein complexes. Their loss of function impacts on mitochondria activities and movements.

For several PD-associated genes, opposite phenotypes on contact sites have been reported, which may depend on the expression levels of the mutated proteins, the type of mutation and the cell nature but also on the characteristics of the contact (i.e., short or long) and of its tethering complexes.

Several important questions remained to be elucidated, among which the possibility that the modulation of one pair organelle contact also impacts on different pairs. A better comprehension of mechanistic details underlying inter-organelle communication will provide new insights into cell homeostasis and metabolism adaptation in response to different stimuli as well as will open new perspectives for tackling PD progression.

Credit Author Statement

Caterina Peggion and Lucia Barazzuol: Data curation, Writing-Original draft preparation. **Elena Poggio**: Figure preparation and critical reading. **Marisa Brini and Tito Calì**: Supervision: **Marisa Brini and Tito Calì**: Writing- Reviewing and Editing.

Declaration of Competing Interest

Authors report no conflicts of interest.

Data availability

No data was used for the research described in the article.

Acknowledgments

Research in the laboratory of the authors is supported by grants from the Ministry of University and Research (Bando SIR 2014 no. RBSI14C65Z and PRIN2017 to T.C) and from the Università degli Studi di Padova (Progetto Giovani 2012 no. GRIC128SP0 to T.C., Progetto di Ateneo 2016 no. CALI_SID16_01 to T.C., STARS Consolidator Grant 2019 to T.C. and Progetto di Ateneo 2015 no. CPDA153402 to M.B) and from PNRR – CN3 National Center for Gene Therapy and Drugs based on RNA Technology to M.B. and T.C. n. CN00000041 (2022-26).

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