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Review

Peroxiredoxins in Mitochondrial Dysfunction and Endoplasmic Reticulum Stress: Implications for Neurodegenerative Diseases

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Abstract

Mitochondrial dysfunction and endoplasmic reticulum (ER) stress are increasingly recognized as coupled, rather than independent, contributors to neurodegeneration, converging at ER–mitochondria contact sites (MERCs) that coordinate Ca^{2+} transfer, redox signaling, and mitochondrial dynamics. Disruption of this crosstalk is implicated in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Peroxiredoxins (PRDXs), a family of thiol-dependent peroxidases distributed across distinct subcellular compartments, are positioned to regulate this inter-organelle crosstalk in an isoform-specific manner. This review summarizes evidence that ER-resident PRDX4 supports oxidative protein folding and limits ER stress signaling, mitochondrial PRDX3 restricts peroxide accumulation and mitochondrial oxidative injury, and PRDX2 and PRDX5 regulate ER–mitochondria coupling through effects on mitochondrial trafficking and mitochondrial fission, respectively, although neither is a core structural component of MERCs. We also discuss how PRDX-dependent suppression of ER and oxidative stress may relate to mitochondrial quality control and mitophagy, and how these mechanisms may relate to MERC dysfunction across AD, PD, and ALS. Overall, the evidence suggests that PRDXs act as organelle-specific redox regulators whose loss may contribute to ER–mitochondria dysfunction, and that restoring or supporting PRDX activity represents a possible therapeutic direction.

Keywords: peroxiredoxins; endoplasmic reticulum stress; mitochondrial dysfunction; ER–mitochondria contact sites; oxidative stress; neurodegenerative diseases

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1. Introduction

Neurodegenerative diseases, which include Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), are characterized by progressive dysfunction and loss of neurons. These disorders predominantly affect older adults, and their prevalence is expected to rise further as the global population continues to age. Despite substantial advances in understanding their molecular and cellular mechanisms, effective preventive or curative treatments remain limited [1]. Therefore, elucidating the pathogenic mechanisms underlying neurodegeneration and identifying novel therapeutic targets remain urgent priorities.

Accumulating evidence indicates that mitochondrial dysfunction and endoplasmic reticulum (ER) stress are closely involved in the onset and progression of neurodegenerative diseases. Importantly, these processes are mechanistically interconnected and form a bidirectional and self-amplifying pathogenic cycle. Mitochondrial dysfunction leads to

excessive production of mitochondrial reactive oxygen species (mtROS), impaired ATP generation, disrupted mitochondrial dynamics, and reduced Ca^{2+}-buffering capacity, all of which can compromise ER protein folding and disturb intracellular Ca^{2+} homeostasis [2]. In turn, persistent ER stress and dysregulated unfolded protein response (UPR) signaling promote Ca^{2+} release from the ER, mitochondrial Ca^{2+} overload, oxidative stress, and activation of apoptotic pathways. Consequently, disruption of ER–mitochondria communication accelerates proteostatic failure, bioenergetic impairment, and neuronal cell death. Sustained or maladaptive UPR activation has therefore emerged as a major pathological feature across multiple neurodegenerative diseases [3].

Peroxiredoxins (PRDXs) are a ubiquitous family of thiol-dependent antioxidant enzymes that reduce hydrogen peroxide, organic hydroperoxides, and peroxynitrite. Based on the number and position of the conserved cysteine residues involved in catalysis, the six mammalian PRDX isoforms are classified into typical 2-Cys PRDXs (PRDX1–PRDX4), an atypical 2-Cys PRDX (PRDX5), and a 1-Cys PRDX (PRDX6) [4]. Individual PRDX isoforms also exhibit distinct subcellular localization patterns. PRDX1 and PRDX2 are predominantly cytosolic, PRDX3 is localized mainly to the mitochondrial matrix, and PRDX4 resides primarily within the ER lumen. PRDX5 is distributed among several compartments, including mitochondria, peroxisomes, the cytosol, and the nucleus, whereas PRDX6 is predominantly cytosolic but also associated with lysosomal and membrane compartments. This spatial compartmentalization enables PRDXs to regulate organelle-specific redox environments rather than functioning solely as general ROS-scavenging enzymes [5,6].

Beyond their canonical antioxidant activity, PRDXs also function as redox sensors, signaling mediators, molecular chaperones, and regulators of cellular stress responses, thereby contributing to the maintenance of ER and mitochondrial homeostasis. For example, ER-resident PRDX4 supports oxidative protein folding by eliminating H_2O_2 generated during disulfide bond formation [7], while mitochondrial PRDX3 and PRDX5 protect mitochondrial function, bioenergetics, and quality control from oxidative stress [8]. Other PRDX isoforms also contribute to ER stress responses, inflammatory signaling, autophagy, and apoptotic cell death [4,5]. Thus, the compartment-specific distribution of PRDXs enables them to coordinate redox regulation, proteostasis, Ca^{2+} signaling, and organelle homeostasis within distinct subcellular environments.

In this review, we summarize recent advances in understanding the isoform-specific roles of PRDXs in regulating ER stress, mitochondrial dysfunction, and ER–mitochondria crosstalk. We examine how ER stress-driven apoptotic cascades, ROS-induced dysregulation of Ca^{2+} signaling, and impaired mitochondrial quality control collectively drive neurodegenerative pathology, and how changes in PRDX expression and subcellular localization regulate these processes at the ER-mitochondrial interface. Finally, we discuss the therapeutic potential of targeting PRDX-dependent pathways to restore organelle homeostasis and disrupt the pathogenic crosstalk between ER stress and mitochondrial dysfunction in neurodegenerative diseases.

Several recent reviews have addressed PRDX biology in the nervous system, including isoform-specific PRDX functions across neuronal development and degeneration [5], as well as broader surveys of PRDXs in neurodegenerative disease [9] and of redox regulation of ER–mitochondria contact sites more broadly [2] or specifically in the context of neurodegeneration [3]. These reviews have largely organized the evidence by individual PRDX isoform, by disease entity, or by neuronal life-cycle stage. The present review instead organizes the evidence around the ER–mitochondria interface itself, positioning PRDX4 at the ER side of this axis, PRDX3 within the mitochondrial matrix, and PRDX2 and PRDX5 as regulators of the functional coupling between the two organelles, through PRDX2-mediated mitochondrial trafficking and MERC remodeling and through PRDX5-

mediated Ca^{2+}/calcineurin–DRP1-dependent mitochondrial fission, respectively. Although six PRDX isoforms are expressed in mammals, this review focuses on PRDX2, PRDX3, PRDX4, and PRDX5, for which mechanistic links to the ER–mitochondria interface have been reported; PRDX1 and PRDX6 are addressed separately in the Conclusion, reflecting the comparatively limited direct evidence currently available for their involvement in this specific inter-organelle axis.

Relevant literature was identified through searches of PubMed up to October 2026, using combinations of terms related to peroxiredoxins, ER stress, mitochondrial dysfunction, ER–mitochondria contact sites, and neurodegenerative diseases. Primary experimental studies were prioritized when evaluating isoform-specific molecular mechanisms, while relevant reviews were consulted to provide broader biological context.

2. ER Stress Signaling: From an Adaptive Survival Response to Inflammation and Apoptosis

The ER is an extensive, interconnected membrane network that serves as a major site of protein synthesis, folding, and post-translational modification. In addition, the ER plays critical roles in Ca^{2+} storage, lipid metabolism, and cellular stress responses. Disturbances in ER function or integrity lead to ER stress, which can be triggered by the accumulation of unfolded or misfolded proteins, alterations in ER Ca^{2+} homeostasis, oxidative stress, and metabolic perturbations. To restore ER homeostasis, cells activate the unfolded protein response (UPR), an integrated signaling network that initially promotes cellular adaptation and survival [2,10,11].

2.1. ER Stress and the Adaptive UPR

The UPR is primarily mediated by three ER membrane-associated stress sensors: activating transcription factor 6 (ATF6), inositol-requiring enzyme 1α (IRE1α), and protein kinase R-like ER kinase (PERK) [10]. Under basal conditions, the luminal domains of these sensors are associated with the ER chaperone glucose-regulated protein 78 (GRP78)/immunoglobulin heavy-chain-binding protein (BiP). Upon ER stress, the preferential sequestration of BiP by accumulated unfolded proteins is thought to promote its dissociation from IRE1α, PERK, and ATF6, thereby facilitating sensor activation and triggering downstream UPR signaling [11,12]. Furthermore, recent structural evidence suggests that direct binding of unfolded polypeptides to the luminal domain of IRE1α also actively contributes to sensor activation [13].

Under mild or transient ER stress, the UPR predominantly activates adaptive responses that reduce the burden of misfolded or unfolded proteins and restore ER function. Activation of IRE1α induces its oligomerization and autophosphorylation, thereby stimulating its endoribonuclease activity. Phosphorylated IRE1α catalyzes the unconventional splicing of X-box-binding protein 1 (XBP1) mRNA to generate the transcriptionally active spliced form, XBP1s [2]. XBP1s translocates to the nucleus and induces expression of genes encoding ER chaperones and components involved in lipid biosynthesis and ER-associated degradation (ERAD), thereby enhancing the cellular capacity to mitigate misfolded protein stress [14]. PERK is similarly activated through oligomerization and autophosphorylation during ER stress. Activated PERK phosphorylates eukaryotic initiation factor-2α (eIF2α) at Ser51, leading to transient attenuation of global mRNA translation and thereby reducing the protein-folding load on the ER. Despite this general translational repression, phosphorylated eIF2α selectively promotes translation of activating transcription factor 4 (ATF4), which upregulates genes involved in amino acid metabolism, antioxidant defense, autophagy, and stress adaptation [15]. Upon ER stress, ATF6 is transported from the ER to the Golgi apparatus, where it is sequentially cleaved by site-1 and site-2 proteases. The resulting

cytosolic N-terminal fragment of ATF6 translocates to the nucleus and binds ER stress-response elements (ERSEs), inducing the expression of ER chaperones, including BiP and GRP94, as well as ERAD components and XBP1 [11,16]. Collectively, activation of IRE1α, PERK, and ATF6 increases protein-folding capacity, reduces ER protein load, and promotes restoration of cellular homeostasis (Figure 1).

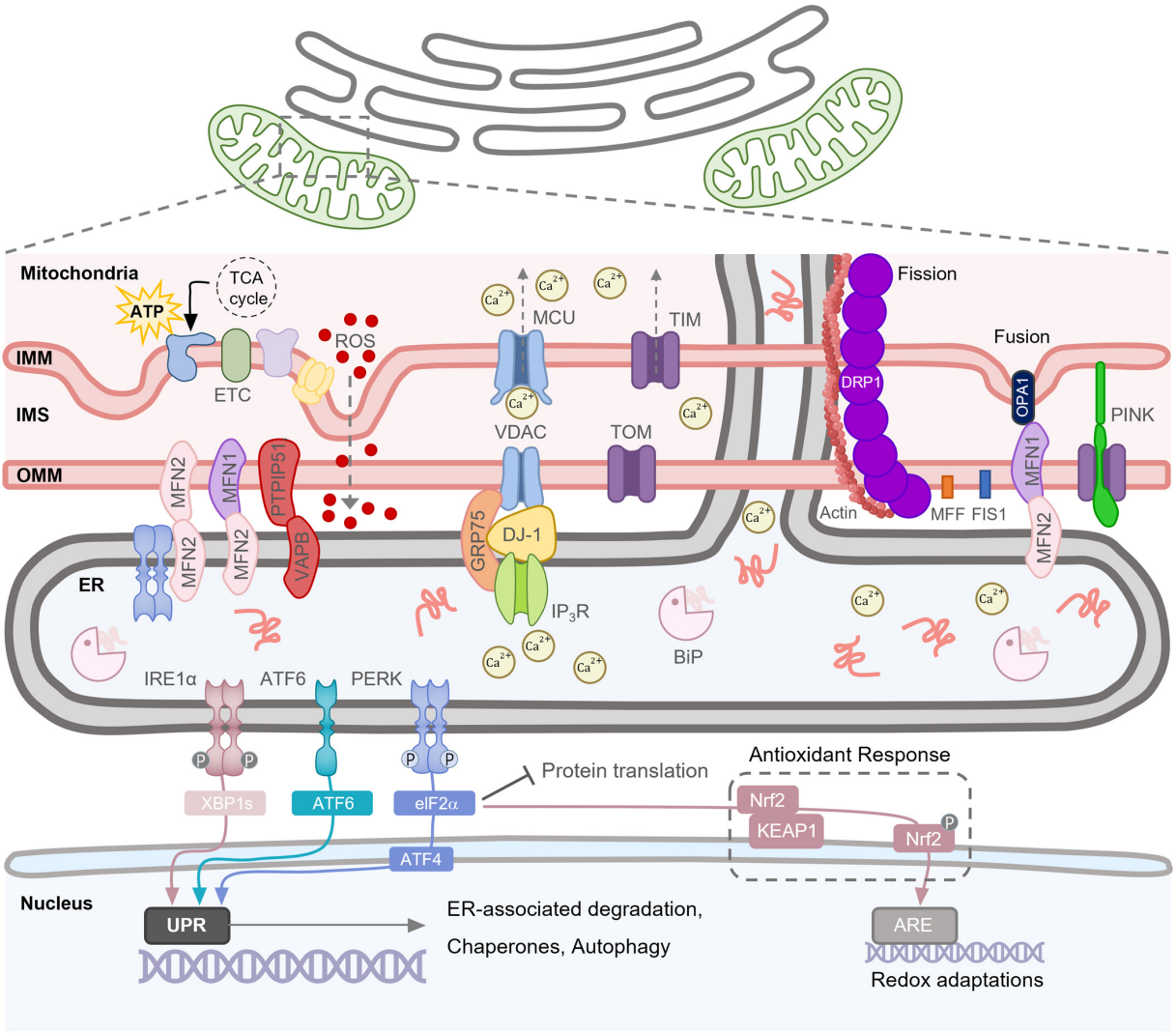

Figure 1. Overview of the ER–mitochondria interface and its regulatory machinery. ER–mitochondria contact sites (MERCs) are physically stabilized by tethering complexes, including the homotypic MFN2–MFN2 and heterotypic MFN2–MFN1 mitofusin tethers (whose precise contribution to MERC tethering remains debated; see Section 3.1), the VAPB–PTPIP51 tether, and the GRP75–DJ-1-stabilized IP3R–VDAC1 Ca^{2+}-transfer complex. Ca^{2+} released from the ER through IP3R crosses the OMM via VDAC1 and is taken up into the mitochondrial matrix through the mitochondrial Ca^{2+} uniporter (MCU), supporting TCA-cycle activity and ATP production. Electron leakage from the electron transport chain (ETC) generates mitochondrial ROS. Mitochondrial morphology is governed by opposing fission (DRP1 oligomerization on actin filaments, recruited via the OMM adaptors MFF and FIS1) and fusion (OPA1-mediated inner-membrane fusion together with MFN1/MFN2-mediated outer-membrane fusion) machinery. At the ER membrane, the three canonical UPR sensors—IRE1α, ATF6, and PERK—converge on downstream transcriptional programs that induce ER-associated degradation, chaperone expression, and autophagy; PERK additionally phosphorylates Nrf2, releasing it from KEAP1 to drive antioxidant response element (ARE)-dependent transcription of redox-adaptive genes. The chaperone BiP engages misfolded proteins in the ER lumen.

2.2. Transition from Adaptive to Terminal UPR

When ER stress is prolonged or unresolvable, the UPR shifts from an adaptive response toward pro-apoptotic and pro-inflammatory signaling cascades. Persistent activation of IRE1α recruits TNF receptor-associated factor 2 (TRAF2), initiating downstream signaling that promotes both apoptotic and inflammatory responses. The IRE1α–TRAF2 complex activates apoptosis signal-regulating kinase 1 (ASK1), which in turn induces the phosphorylation and activation of c-Jun N-terminal kinase (JNK) [17]. Activated JNK promotes the mitochondrial translocation and activation of the pro-apoptotic protein BAX and facilitates BAX/BAK oligomerization at the outer mitochondrial membrane (OMM).

This process induces mitochondrial outer membrane permeabilization (MOMP), resulting in the cytosolic release of cytochrome c, formation of the apoptosome, and subsequent activation of the caspase cascade [2,18]. Simultaneously, persistent UPR signaling promotes inflammatory responses by activating nuclear factor-κB (NF-κB). IRE1α–TRAF2-dependent signaling contributes to activation of the IκB kinase (IKK) complex, leading to phosphorylation and degradation of IκB and subsequent nuclear translocation of NF-κB. In addition, PERK-dependent translational attenuation can contribute to NF-κB activation by reducing synthesis of the short-lived inhibitor IκB. Nuclear NF-κB subsequently drives transcriptional upregulation of pro-inflammatory cytokines and other immune-response genes, thereby linking unresolved ER stress to chronic inflammation [2,19].

Chronic ER stress also directly couples UPR activation to mitochondrial apoptotic pathways. Sustained activation of PERK and ATF6 pathways plays a pivotal role in ER stress-induced apoptosis through the transcriptional induction of C/EBP-homologous protein (CHOP) [11]. CHOP downregulates the anti-apoptotic protein BCL-2 while upregulating the pro-apoptotic protein BIM, thereby facilitating BAX/BAK-dependent MOMP and downstream caspase activation [20]. Chronic ER stress is also closely associated with oxidative damage and inflammasome activation via the CHOP–thioredoxin-interacting protein (TXNIP) axis. CHOP has been shown to increase TXNIP expression and promote its translocation from the nucleus to mitochondria [21]. Mitochondrial accumulation of TXNIP disrupts the thioredoxin redox system and increases mitochondrial ROS production. These alterations facilitate NLRP3 inflammasome activation, particularly under persistent mitochondrial oxidative stress, leading to caspase-1 activation and subsequent maturation and release of the pro-inflammatory cytokines IL-1β and IL-18 [22].

Prolonged IRE1α RNase activity also engages regulated IRE1α-dependent decay (RIDD), leading to the cleavage and degradation of selected ER-associated mRNAs—including those encoding ER chaperones—as well as microRNAs such as miR-17, miR-34a, miR-96, and miR-125b, which normally repress translation of the pro-apoptotic protease caspase-2. By derepressing caspase-2 translation, hyperactivated RIDD shifts IRE1α signaling away from supporting adaptive protein folding toward promoting apoptotic cell death [23]. Furthermore, IRE1α-mediated degradation of miR-17 relieves the post-transcriptional repression of TXNIP, leading to elevated TXNIP expression and subsequent activation of the NLRP3 inflammasome [24]. Thus, unresolved ER stress simultaneously promotes apoptotic cell death and inflammatory signaling, providing a crucial mechanistic link between proteostatic failure and disease progression (Figure 2). The contribution of compartment-specific PRDX isoforms to these oxidative stress-associated signaling pathways is further discussed in Section 4.

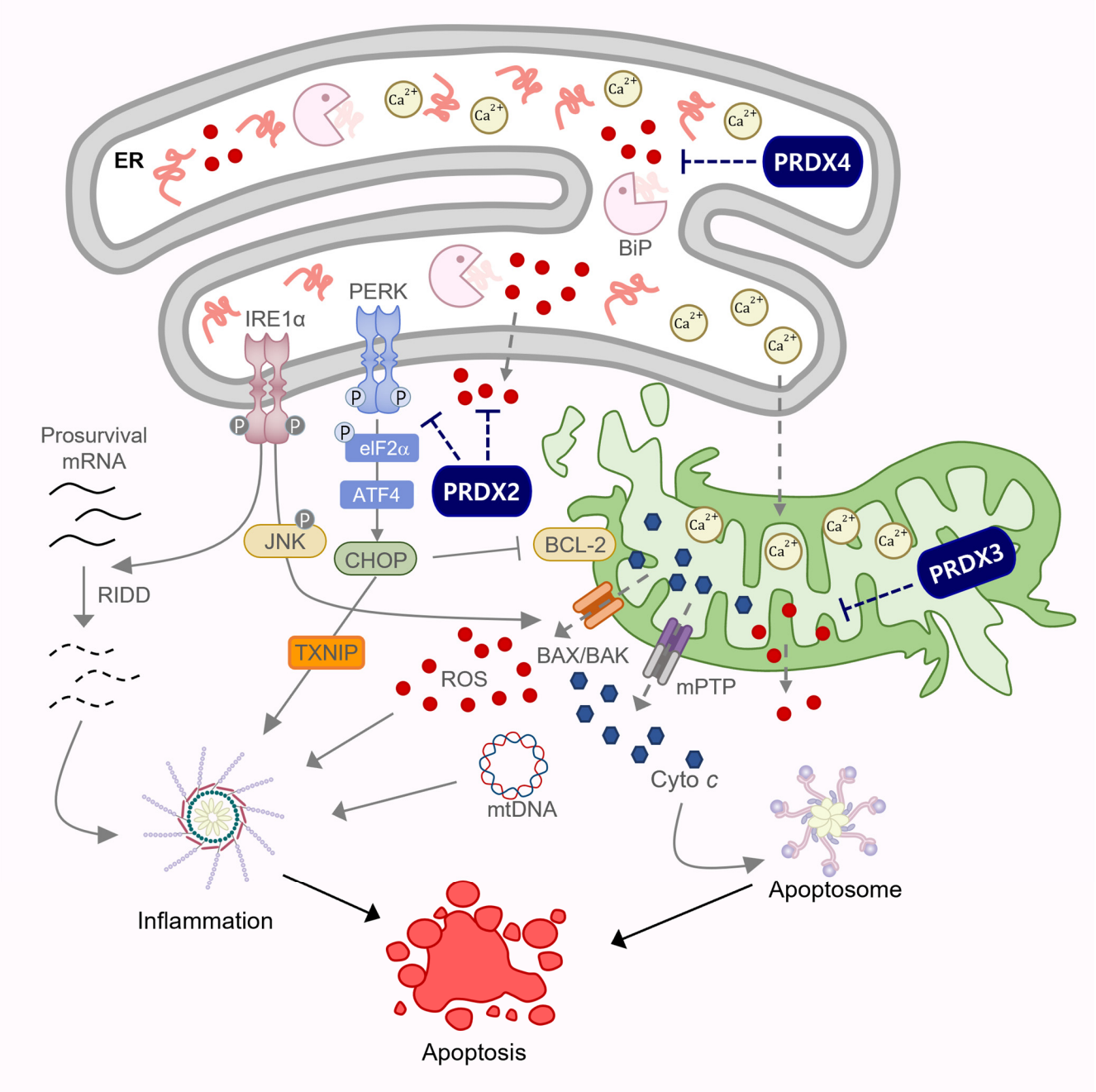

Figure 2. ER stress-induced apoptotic and inflammatory signaling. Under unresolved ER stress, IRE1α branches into two outputs: regulated IRE1-dependent decay (RIDD) degrades prosurvival mRNAs, contributing to NLRP3 inflammasome activation, while IRE1α–JNK signaling promotes BAX/BAK activation. In parallel, PERK–eIF2α–ATF4 signaling induces CHOP, which downregulates BCL-2 and, via the TXNIP–ROS axis, activates the NLRP3 inflammasome. At the mitochondrion, BAX/BAK-dependent outer membrane permeabilization releases cytochrome c to form the apoptosome, while opening of the mitochondrial permeability transition pore (mPTP) releases additional ROS and mitochondrial DNA (mtDNA), the latter further activating the NLRP3 inflammasome. The apoptosome and NLRP3 inflammasome pathways converge on apoptotic and inflammatory cell death. PRDX3 and PRDX4 limit mitochondrial and ER-derived oxidative stress, respectively, thereby potentially attenuating downstream apoptotic and inflammatory signaling. Cytosolic PRDX2 reduces ROS accumulation and ER stress-associated PERK–eIF2α signaling, although direct inhibition of PERK phosphorylation by PRDX2 has not been established. Solid inhibitory connectors indicate directly demonstrated relationships, whereas dashed connectors indicate indirect or mechanistically inferred relationships, consistent with the evidence-level classification in Table 1.

Table 1. Compartment-specific PRDX functions and type of evidence for roles at the ER–mitochondria interface in neurodegeneration. Evidence levels refer to the specified ER–mitochondria-related mechanism, not to overall neuroprotective efficacy.

Isoform	Localization	Principal Function	ER-Mitochondria Relevance/Model	Evidence Level
PRDX1	Cytosol, nucleus	General cellular redox signaling	No isoform-specific ER–mitochondria interface data identified to date [4–6]	Evidence gap
PRDX2	Mainly cytosolic	Stress signaling; mitochondrial trafficking	Alcohol-induced MERC remodeling and Ca^{2+} dysregulation in HT22 cells via PERK–Armcx3 axis [25]	Direct
			SIRT1-dependent neuroprotection and reduced plasma PRDX2 levels in PD [26]	Indirect
PRDX3	Mitochondrial matrix	Mitochondrial H_2O_2 detoxification	Protects against MPP^+-induced oxidative stress in SH-SY5Y cells; implicated in AD and PD [8,27,28]	Indirect
			Candidate for AAV/lentiviral PRDX3 gene-therapy delivery in the SOD1 ALS mouse model [29]	Indirect
PRDX4	ER lumen	Peroxide removal; PDI-coupled oxidative folding	Limits ER oxidative stress via PDI-coupled H_2O_2 removal during protein folding [7,30,31]	Indirect
			Protects against amyloid-β- and glutamate-induced ER stress and Ca^{2+} overload in HT-22 cells [32,33]	Indirect
PRDX5	Mitochondria, peroxisomes, cytosol	Redox protection; fission-associated signaling	Blocks Ca^{2+}-dependent calpain/Bax activation and caspase-9-mediated mitochondrial apoptosis in MPP^+-treated neurons [34]	Indirect
			Preserves DRP1 Ser637 phosphorylation and prevents ER–mitochondria/DRP1 colocalization under iron overload in HT-22 cells [35]	Direct
			Protects against iron-overload-induced hippocampal neuronal loss in PRDX5-deficient mice in vivo [36]	Indirect
			Suppresses ERK–DRP1-dependent mitochondrial fragmentation induced by amyloid- β oligomers in HT-22 cells [37]	Indirect
PRDX6	Cytosol, lysosome/membrane	Peroxide and phospholipid redox regulation	No isoform-specific ER–mitochondria interface data identified to date [4–6]	Evidence gap
			Up-regulated (~4-fold) in reactive astrocytes in the SOD1 ALS mouse model (compensatory) [38]	Indirect
			Nrf2–ARE-inducible in non-neuronal cell models (pharmacologically tractable target) [39]	Indirect

Evidence levels: direct, structural or functional evidence for altered ER–mitochondria contact-site (MERC) morphology, tethering, or coupling; indirect, demonstrated regulation of compartment-specific (ER or mitochondrial) oxidative stress, Ca2+ signaling, or cell survival without direct evidence of MERC structural change; evidence gap, no isoform-specific data in the ER–mitochondria interface context identified to date.

2.3. ER Redox Homeostasis and Oxidative Stress

The ER maintains a more oxidizing environment than the cytosol, which supports the formation and rearrangement of disulfide bonds required for proper protein folding. During oxidative protein folding, protein disulfide isomerases (PDIs) catalyze thiol–disulfide exchange reactions and are subsequently reoxidized by ER oxidoreductin 1 (ERO1), which transfers electrons to molecular oxygen and generates H_2O_2 as a by-product [40]. In addition to this folding-coupled ROS production, NADPH oxidase 4 (NOX4), which is enriched in the ER membrane in many cell types, constitutes a further, folding-independent source of ER-derived ROS and can markedly increase H_2O_2 production under stress conditions [30].

As the principal ER-resident peroxidase, PRDX4 detoxifies H_2O_2 generated from both ERO1-mediated oxidative folding and NOX4 activity [7,31]. Upon reacting with H_2O_2, the peroxidatic cysteine of PRDX4 is oxidized to a sulfenic acid, which then condenses to form a resolving disulfide bond. Unlike most peroxiredoxins, which are recycled via the classical thioredoxin system, oxidized PRDX4 instead transfers its oxidizing equivalents directly to PDI via thiol–disulfide exchange, thereby regenerating itself and enabling PDI to form new disulfide bonds. Through this redox relay, PRDX4 simultaneously eliminates H_2O_2 and actively drives oxidative protein folding, rather than merely functioning as a passive antioxidant [41].

Under physiological conditions, ER redox homeostasis is tightly regulated to maintain an appropriate balance between oxidative protein folding and antioxidant capacity. However, excessive ROS production or increased protein-folding demand can disrupt disulfide bond formation, impair chaperone and oxidoreductase function, and promote the accumulation of misfolded proteins. This creates a self-amplifying cycle of oxidative stress and proteostatic failure that sustains ER stress and UPR activation [29–31]. ER redox status also directly shapes UPR signaling through redox-sensitive thiol–disulfide exchange: members of the PDI family modulate the conformational and redox states of IRE1α, PERK, and ATF6, whereby PDIA5 supports the redox-dependent trafficking of ATF6 from the ER to the Golgi [42], PDIA6 attenuates IRE1α signaling through disulfide-dependent association [43], and PDI itself functions as a redox-sensitive activator of PERK [44]. Thus, ER-derived ROS act not only as damaging by-products but also as signaling mediators that modulate the intensity and outcome of the UPR. As discussed below, this redox-signaling axis extends to ER Ca^{2+} handling as well, since ROS-generating oxidoreductases such as ERO1α also directly modulate inositol 1,4,5-trisphosphate receptors (IP3R) channel activity, linking ER redox imbalance to downstream Ca^{2+} dysregulation and mitochondrial dysfunction.

2.4. ER Stress-Induced Ca^{2+} Dysregulation

The ER serves as the major intracellular Ca^{2+} reservoir and plays a central role in maintaining cellular Ca^{2+} homeostasis. ER Ca^{2+} levels are regulated by a coordinated network of pumps, channels, and Ca^{2+}-buffering chaperones—including calreticulin, calnexin, BiP, and GRP94—whose protein-folding activity depends on an appropriate ER Ca^{2+} concentration. Ca^{2+} uptake into the ER is primarily mediated by sarco/endoplasmic reticulum Ca^{2+}-ATPases (SERCA) in an ATP-dependent manner, whereas Ca^{2+} release from the ER is mainly mediated by IP3R and ryanodine receptors (RyR) [45]. During ER stress, ER Ca^{2+} depletion occurs through impaired SERCA activity, hyperactivated IP3R/RyR gating, and increased ER Ca^{2+} leakage. Loss of ER Ca^{2+} homeostasis compromises Ca^{2+}-dependent chaperone function, thereby impairing protein folding and further aggravating ER stress [2,45].

Persistent UPR signaling can further aggravate Ca^{2+} dysregulation through the PERK–ATF4–CHOP pathway. CHOP induces ERO1α expression, thereby altering the redox state and activity of IP3Rs and promoting ER Ca^{2+} release [46]. This CHOP-driven induction of ERO1α further exacerbates the aforementioned intrinsic H_2O_2 production, thereby coupling CHOP-mediated oxidative stress in the ER directly to the Ca^{2+} dysregulation described here [40,46]. Excessive Ca^{2+} release from the ER into the cytosol can activate Ca^{2+}-dependent proteases such as calpains and contribute to apoptotic signaling. In rodent cells, calpain activation has also been linked to cleavage and activation of caspase-12, an ER-associated caspase implicated in ER stress-induced apoptosis [47]. More importantly, enhanced ER Ca^{2+} release also increases Ca^{2+} transfer to mitochondria at ER–mitochondria contact sites (MERCs), providing a direct mechanistic bridge between ER stress and mitochondrial dysfunction.

3. Mitochondrial Dysfunction and ER-Mitochondria Crosstalk

Mitochondria are essential, multifunctional organelles that generate the majority of cellular adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) and regulate diverse aspects of cellular metabolism. Beyond their central role in bioenergetics, mitochondria function as intracellular signaling hubs by regulating ROS production, Ca^{2+} homeostasis, and cell survival pathways. Mitochondrial homeostasis is maintained through an integrated quality-control network involving mitochondrial fission and fusion, biogenesis, and the selective removal of damaged mitochondria by mitophagy [48]. Disruption of these processes leads to the accumulation of dysfunctional mitochondria, excessive ROS production, impaired ATP generation, and altered Ca^{2+} handling. Accordingly, mitochondrial dysfunction is closely associated with the pathogenesis and progression of various human diseases, particularly neurodegenerative disorders [49].

Mitochondria are also highly dynamic organelles that communicate with other intracellular compartments, including the ER, nucleus, and lysosomes, to coordinate cellular metabolism, stress signaling, and survival. Among these inter-organelle interactions, MERCs are specialized regions of close membrane apposition associated with mitochondria-associated membranes (MAMs), which are enriched in proteins that regulate ER-mitochondria communication [50]. These contact sites facilitate the coordinated regulation of Ca^{2+} transfer, lipid metabolism, mitochondrial dynamics, autophagy, and apoptotic signaling [2,10]. Therefore, alterations in the structural and functional integrity of ER–mitochondria contacts can profoundly affect mitochondrial homeostasis and cellular stress responses.

3.1. ER-Mediated Mitochondrial Ca^{2+} Overload

MERCs are physically organized and maintained by specific tethering complexes that bridge the ER and the OMM. The most extensively characterized of these is the mitofusin-based tether formed between ER-localized MFN2 and mitochondrial MFN2 or MFN1. Assembly of this complex depends on the physical interaction between MFN2 and PERK at the ER membrane; disrupting either component reduces MERC coverage, whereas loss of MFN2 dysregulates the PERK–ATF4–CHOP axis and destabilizes mitochondrial Ca^{2+} handling and organellar morphology [2]. However, the precise role of MFN2 in MERC organization remains debated: different experimental approaches have reported both decreased and increased ER–mitochondria contacts following MFN2 loss, suggesting that its function at this interface may be context- or method-dependent rather than a single, universally established tethering mechanism [2]. Another distinct structural tether comprises ER vesicle-associated membrane protein B (VAPB) and OMM-anchored protein tyrosine phosphatase interacting protein-51 (PTPIP51); disruption of this VAPB–PTPIP51 interaction delays Ca^{2+} flux into mitochondria and promotes mitochondrial fragmentation, a mechanism implicated in TDP-43-mediated ALS pathogenesis, as detailed in subsequent sections [51]. Within the Ca^{2+}-transfer complex itself, DJ-1 acts together with GRP75 to regulate and stabilize the IP3R– voltage-dependent anion channel 1 (VDAC1) interaction, thereby preserving MERC integrity and Ca^{2+} entry into mitochondria [2,51]. Among the diverse functions of MERCs, Ca^{2+} transfer is the best-characterized mechanism coupling ER activity to mitochondrial bioenergetics [10,52]. Notably, IRE1α has been shown to regulate this ER–mitochondrial Ca^{2+} flux through a non-canonical structural role that operates independently of BiP dissociation or UPR activation. At MAMs, basal IRE1α functions as a structural scaffold that stabilizes the IP3R complex, maintaining constitutive Ca^{2+} transfer to sustain TCA cycle activity and ATP production [53]. This IRE1α-supported Ca^{2+} flux therefore represents a physiological mechanism through which the ER continuously fuels mitochondrial bioenergetics under normal conditions [52,53].

However, during prolonged ER stress, this regulated Ca^{2+} transfer becomes excessive and pathological. Enhanced ER Ca^{2+} efflux at MERCs enables Ca^{2+} released through IP3Rs to be efficiently shuttled to the outer mitochondrial membrane via the IP3R-GRP75-VDAC1 tethering complex, where it subsequently enters the mitochondrial matrix through the mitochondrial Ca^{2+} uniporter (MCU) [10,11,54]. Although physiological mitochondrial Ca^{2+} uptake supports normal oxidative metabolism and ATP production, pathological Ca^{2+} accumulation causes mitochondrial Ca^{2+} overload, accelerates mitochondrial ROS generation, and disrupts the mitochondrial membrane potential. This promotes opening of the mitochondrial permeability transition pore (mPTP), cytosolic release of cytochrome c, and subsequent activation of the caspase signaling cascade and pro-apoptotic pathways [55]. These events lead to bioenergetic failure and increase susceptibility to mitochondrial-dependent cell death. Thus, dysregulated Ca^{2+} signaling constitutes a key pathway through which prolonged ER stress propagates mitochondrial dysfunction and amplifies cellular injury (Figure 3). PRDX5-dependent regulation of this Ca^{2+}-transfer axis and its downstream effects on mitochondrial fission is discussed in Section 4.3.

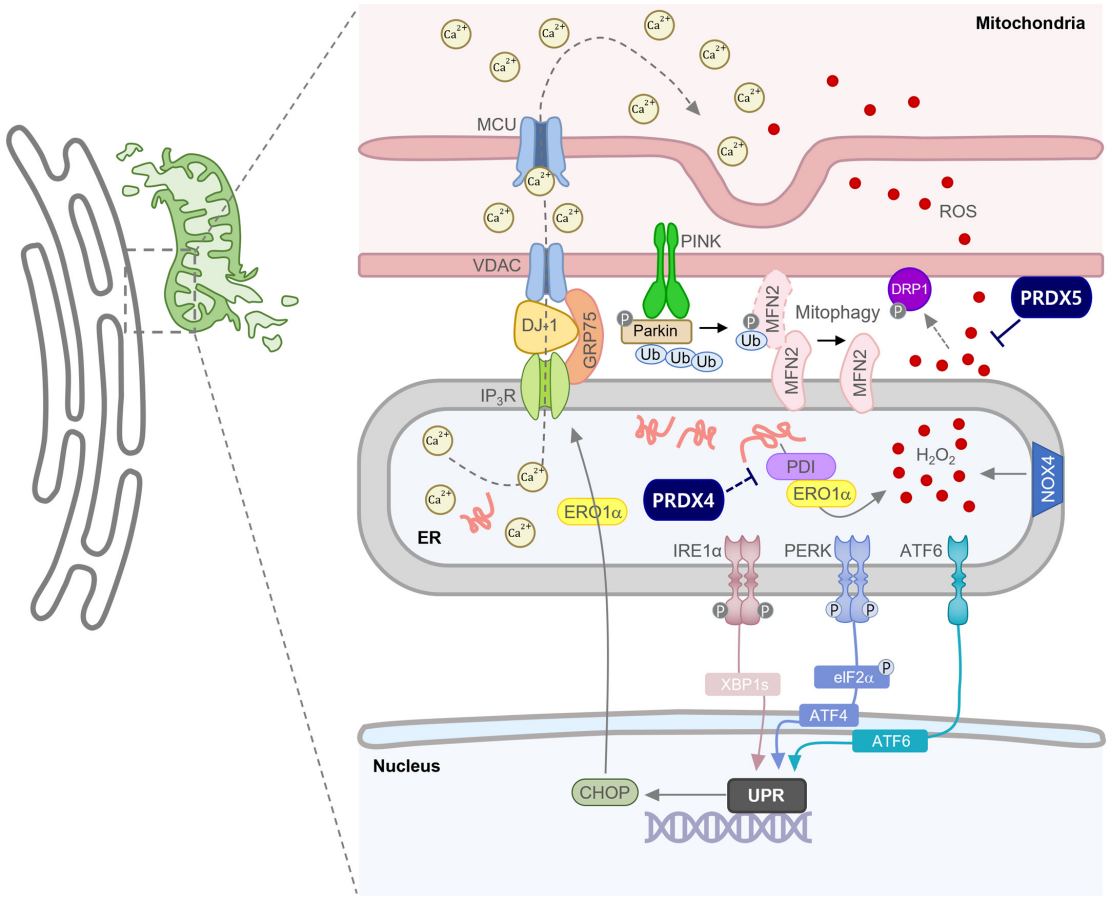

Figure 3. The Ca^{2+}-transfer complex, PINK1/Parkin-dependent mitophagy initiation, and ER redox signaling at the MERC. The GRP75–DJ-1–IP3R–VDAC1–MCU axis mediates Ca^{2+} transfer from the ER to the mitochondrial matrix. At the OMM, PINK1 phosphorylates Parkin, which polyubiquitinates the ER-tethering pool of MFN2 to initiate mitophagy. Within the ER, the PDI–ERO1α oxidative protein-folding couple and NOX4 both generate H_2O_2. ERO1α further oxidizes IP3R, enhancing its Ca^{2+}-release activity and linking ER redox status to mitochondrial Ca^{2+} signaling. PRDX5 modulates ROS-associated mitochondrial fission at this interface, although its direct involvement in PINK1/Parkin-dependent mitophagy initiation remains to be established. PRDX4 constrains ER-derived ROS at this interface by limiting local H_2O_2 accumulation. As in Figure 2, solid and dashed connectors denote directly demonstrated and indirect/inferred relationships, respectively (see Table 1).

3.2. Redox Crosstalk Between the ER and Mitochondria

ER–mitochondria communication is tightly coupled to redox homeostasis because both organelles are major sources and targets of ROS. While the ER generates H_2O_2 during ERO1-driven oxidative folding, mitochondria produce ROS through electron transport chain leakage—a physiological ROS pool essential for adaptive stress responses under basal conditions [54]. This localized redox state directly dictates MERC Ca^{2+} flux: as noted above, ERO1α-mediated oxidative modification of IP3Rs enhances their Ca^{2+}-release activity, thereby increasing Ca^{2+} flux from the ER to mitochondria [46]. When this redox-enhanced Ca^{2+} flux becomes excessive, it drives mitochondrial Ca^{2+} overload and mPTP-mediated apoptotic signaling, while accelerating mtROS generation. The resulting mtROS can diffuse back to the ER, where they oxidize luminal chaperones and Ca^{2+}-handling proteins, impairing Ca^{2+} regulation and protein-folding capacity. Through this reciprocal exchange, ER-derived ROS and mtROS form a bidirectional redox-Ca^{2+} amplification loop that progressively compromises both organelles [10,54]. Notably, organelle-targeted peroxiredoxins—specifically mitochondrial PRDX3 and PRDX5, coupled with ER-resident PRDX4—are positioned to constrain this feed-forward loop by limiting local H_2O_2 accumulation, as detailed below.

Redox-sensitive UPR signaling further shapes this inter-organelle crosstalk. Upon initial ER stress, PERK forms a redox-dependent heterocomplex with ERO1α via the oxidoreductase's C-terminal active site and Cys216 of PERK, promoting the oxidation of MAM-resident proteins and enhancing ER–mitochondrial Ca^{2+} flux [55]. IRE1α is similarly subject to redox regulation at MAMs, where the ROS-sensitive chaperone sigma-1 receptor stabilizes IRE1α under ER stress to sustain its structural role in ER–mitochondrial Ca^{2+} transfer [56]. Through these mechanisms, UPR sensors couple ER redox status directly to mitochondrial Ca^{2+} handling and bioenergetic output. When sustained, this reciprocal redox signaling triggers a self-amplifying cascade of Ca^{2+} dysregulation, mtROS accumulation, proteostatic failure, and bioenergetic dysfunction, ultimately promoting apoptotic cell death. In parallel with these pro-oxidant pathways, PERK orchestrates an adaptive antioxidant response at MERCs. PERK-mediated phosphorylation of nuclear factor erythroid 2-related factor 2 (Nrf2) triggers its dissociation from the cytosolic inhibitor Keap1, facilitating Nrf2 nuclear translocation and activation of antioxidant response element (ARE)-driven transcription of genes such as thioredoxin, glutathione synthetase, glutathione S-transferase, and ferritin. Crucially, loss of PERK impairs this Nrf2 activation and increases ROS accumulation [2,11,57]. This PERK–Nrf2–ARE axis, therefore, constitutes a redox-adaptive, cytoprotective arm of UPR signaling at MERCs that is mechanistically distinct from the pro-oxidant PERK–ERO1α and IRE1α–sigma-1 receptor mechanisms.

3.3. Mitochondrial Dynamics and Quality Control

ER–mitochondrial contact sites also participate in regulating mitochondrial dynamics and quality control. Mitochondrial morphology is continuously remodeled through a balance between fission and fusion, mediated primarily by dynamin-related protein 1 (DRP1) together with its outer-membrane receptor mitochondrial fission factor (MFF) and fission protein 1 (FIS1), MFN1/2, and optic atrophy 1 (OPA1) [48,58]. Specifically, ER tubules mark sites of mitochondrial constriction and facilitate DRP1-dependent fission, whereas MFN1/2 and OPA1 mediate outer and inner mitochondrial membrane fusion, respectively. MERCs additionally serve as platforms for autophagosome formation, thereby supporting the mitophagic clearance of damaged mitochondria [59]. At the molecular level, PINK1 accumulating on depolarized mitochondria phosphorylates MFN2, which recruits Parkin to MERCs. Parkin-mediated ubiquitination of the ER-tethering pool of MFN2 promotes the physical separation of the two organelles and initiates mitophagy, directly linking loss of

MERC tethering to activation of this mitochondrial quality-control pathway [2,60]. ER–mitochondrial contact sites also directly regulate mitochondrial DNA (mtDNA) replication and segregation. Disruption of mitochondrial dynamics can compromise these processes and promote the release of mtDNA into the cytosol [61]. During cellular senescence and sublethal apoptotic stress, MFN2 depletion increases BAX/BAK-dependent minority MOMP and cytosolic mtDNA release, thereby activating the cGAS–STING pathway and driving the senescence-associated secretory phenotype (SASP) [62]. Because MFN2 also mediates ER–mitochondria tethering, MERCs have more broadly been proposed as potential regulatory sites for mtDNA release through channels such as VDAC, located at or near these contacts [2]. Impairment of these MERC-dependent dynamics and quality-control mechanisms exacerbates the bioenergetic and Ca^{2+}-handling defects, further compromising mitochondrial integrity.

Beyond localized crosstalk, mitochondrial stress recruits a dedicated organelle-autonomous stress response, the mitochondrial unfolded protein response (UPRmt), which is cross-regulated by the ER via PERK signaling. Under basal conditions, the transcription factor ATF5 is constitutively imported into the mitochondrial matrix via the TOM/TIM translocase complex and rapidly degraded, thereby serving as a functional sensor of mitochondrial protein import efficiency. When mitochondrial proteostasis is impaired, eIF2α phosphorylation alters ATF5 translational control, driving its nuclear translocation rather than mitochondrial import [63]. PERK-dependent phosphorylation of eIF2α further attenuates mitochondrial protein import under these conditions, reinforcing this redirection of ATF5 to the nucleus, where it converges with ATF4 and CHOP to activate the UPRmt and upregulate mitochondrial chaperones, proteases, and antioxidant genes that restore mitochondrial folding capacity [64]. Therefore, the UPRmt and the ER UPR are coordinately regulated through PERK/eIF2α signaling, providing a mitochondria-intrinsic layer to the ER–mitochondria stress response beyond the Ca^{2+}-, redox-, and dynamics-based mechanisms detailed previously.

Dysregulated ER–mitochondria crosstalk has been increasingly implicated in the pathogenesis of neurodegenerative diseases. In AD, amyloid-β and pathological tau are associated with altered ER–mitochondria Ca^{2+} signaling, mitochondrial fragmentation, oxidative stress, and abnormal lipid metabolism at MERCs [65]. In PD, α-synuclein accumulates at MERCs and disrupts ER–mitochondria Ca^{2+} signaling and mitochondrial morphology, while defects in PINK1/Parkin-dependent mitochondrial quality control impair MERC tethering, mitophagy, and autophagosome formation [66,67]. Similarly, ALS-associated TDP-43 and mutant SOD1 disrupt MAM integrity and ER–mitochondria Ca^{2+} transfer [32,51]. Collectively, these findings underscore that ER stress and mitochondrial dysfunction are mechanistically interconnected drivers of neurodegeneration, with redox imbalance as a central, organelle-linking feature. PRDXs, as compartment-specific redox regulators, are therefore well positioned to modulate this ER–mitochondria stress axis, as examined in detail in the following section.

4. PRDXs in the Regulation of ER–Mitochondria Crosstalk in Neurodegeneration

4.1. PRDX4 and ER Redox Homeostasis

PRDX4 is unique among mammalian PRDX isoforms for its predominant localization to the ER lumen and secretory pathway, where it clears H_2O_2 produced by both ERO1 and NOX4 and directly couples this antioxidant activity to oxidative protein folding through a redox relay with PDI [7,31,41]. PRDX4 thus functions not only as an antioxidant enzyme but also as an integral regulator of ER redox homeostasis and proteostasis. Evidence for PRDX4 at the ER–mitochondria interface is currently indirect: these studies demonstrate

regulation of ER redox homeostasis and its downstream consequences for neuronal survival, rather than direct modulation of MERC structure or tethering itself. Impaired PRDX4 activity can disturb this balance, resulting in excessive ER oxidative stress, defective protein folding, and increased susceptibility to UPR activation. Consistent with this function, PRDX4 attenuation or overexpression directly modulates neuronal survival under acute stress conditions: in HT-22 hippocampal neuronal cells, PRDX4 overexpression markedly attenuated ROS accumulation, ER stress responses, intracellular Ca^{2+} overload, and apoptotic death induced by both amyloid-β oligomers [33] and glutamate excitotoxicity [27]. Conversely, PRDX4 silencing exacerbated these pathological cascades [27,33]. These findings demonstrate that PRDX4 stabilizes the ER side of the ER–mitochondria stress axis by maintaining an appropriate redox environment and preventing the hyperactivation of stress signaling pathways.

4.2. PRDX3 and Mitochondrial Redox Homeostasis

PRDX3 is predominantly localized to the mitochondrial matrix, where it is a primary component of the mitochondrial H_2O_2-detoxifying system [8]. Because mitochondrial respiration continuously generates ROS, particularly when electron transport is impaired, PRDX3 is strategically positioned to limit mitochondrial peroxide accumulation and preserve mitochondrial proteins, membrane integrity, and bioenergetic function. Consequently, loss or functional impairment of PRDX3 increases mitochondrial vulnerability to oxidative stress and can promote mitochondrial-dependent apoptosis [5,8]. As with PRDX4, current evidence for PRDX3 at the ER–mitochondria interface is indirect, reflecting regulation of mitochondrial oxidative stress rather than direct modulation of MERC structure or tethering.

The neuroprotective capacity of PRDX3 is particularly relevant to neurodegenerative pathologies driven by mitochondrial oxidative stress. In human neuroblastoma SH-SY5Y cells, shRNA-mediated silencing of PRDX3 and PRDX5 increased vulnerability to oxidative damage and MPP^+-induced apoptosis, with PRDX3-depleted cells showing elevated protein carbonylation and enhanced MPP^+-induced caspase-3 cleavage relative to control cells [28]. In AD models, PRDX3 expression is reduced in brain tissue, and PRDX3 overexpression attenuates mitochondrial oxidative stress and improves cognitive performance in amyloid precursor protein transgenic mice. In PD, PRDX3 appears to be dysregulated post-translationally rather than at the level of expression. LRRK2 mutations increase PRDX3 phosphorylation, thereby reducing its peroxidase activity, and PRDX3-depleted cells show heightened vulnerability to LRRK2 mutation-associated damage [9]. These findings support the concept that PRDX3 acts as a mitochondrial redox checkpoint that prevents excessive mtROS from amplifying ER stress and other stress-responsive pathways.

4.3. PRDX2 and PRDX5 as Regulators of ER–Mitochondria Communication

Although PRDX2 and PRDX5 are not established structural components of MERCs, accumulating evidence indicates that both isoforms can regulate the functional coupling between the ER and mitochondria by controlling ROS levels, Ca^{2+} homeostasis, mitochondrial transport, and mitochondrial dynamics [4,6,9]. Direct experimental evidence for this relationship comes from recent studies showing that changes in PRDX expression alter MERC formation, thereby influencing mitochondrial function.

PRDX2, which is predominantly cytosolic, has recently been shown to regulate MERCs in neuronal cells. In alcohol-treated HT22 cells, PRDX2 deficiency increased the length of mitochondria-associated ER membranes and the proportion of mitochondria contacting the ER. This structural remodeling led to excessive mitochondrial Ca^{2+} accumulation, loss of mitochondrial membrane potential, and enhanced mitochondria-dependent apoptosis. Notably, chelation of intracellular Ca^{2+} attenuated these abnormalities, supporting the

conclusion that altered Ca^{2+} transfer is a major consequence of PRDX2-dependent changes in ER–mitochondria contacts [25]. Mechanistically, PRDX2 appears to link oxidative and ER stress to mitochondrial positioning and MERC formation. PRDX2-deficient neuronal cells exhibited enhanced PERK signaling and downregulation of Armcx3, a mitochondrial protein that regulates mitochondrial transport via Miro/Trak2 complexes, through an ATF3-miR-181b-5p-Armcx3 axis downstream of ER stress. Pharmacological inhibition of ER stress reversed Armcx3 expression, normalized mitochondrial Ca^{2+} levels, and improved mitochondrial membrane potential. Likewise, reintroduction of PRDX2 restored alcohol-induced mitochondrial dysfunction and hyperactivated PERK signaling. These findings support that PRDX2 controls ER–mitochondria communication primarily through redox-dependent regulation of ER stress and mitochondrial trafficking [25]. However, PRDX2's protective role in PD models is not limited to this MERC-centered mechanism. In MPP^+-treated SH-SY5Y cells, PRDX2 overexpression also reduced ROS accumulation, preserved mitochondrial membrane potential, and increased cell viability and tyrosine hydroxylase expression via a distinct SIRT1-dependent signaling pathway that has not yet been linked to ER stress or MERC function. Furthermore, circulating PRDX2 levels were lower in the plasma of PD patients than in healthy controls [26]. Together, these observations suggest that PRDX2 contributes to neuroprotection against neurodegenerative insults through both MERC-dependent and MERC-independent mechanisms.

PRDX5 provides a second, mechanistically distinct link between oxidative stress and ER-mediated mitochondrial remodeling. In an MPP^+-induced neuronal injury model, mitochondrial PRDX5 overexpression blocked the rise in intracellular Ca^{2+} and Ca^{2+}-dependent activation of calpains and Bax, and attenuated caspase-9-dependent mitochondrial apoptosis, supporting a role for PRDX5 in regulating mitochondria–ER communication during neurotoxic stress [34]. In iron-overloaded HT-22 neuronal cells, ROS accumulation was detected in the ER earlier than in mitochondria, indicating that ER oxidative stress can precede and propagate mitochondrial damage. Iron overload expanded the ER area, activated ER stress, elevated intracellular Ca^{2+} levels, and stimulated calcineurin activation. This calcineurin activation triggered dephosphorylation of DRP1 at Ser637 and its subsequent translocation to mitochondria, driving mitochondrial fragmentation. Moreover, PRDX5 overexpression suppressed ROS accumulation, attenuated ER stress and Ca^{2+}/calcineurin signaling, preserved DRP1 Ser637 phosphorylation, and prevented DRP1 translocation to mitochondria, whereas PRDX5 silencing exacerbated all of these responses [35]. Imaging analysis further showed increased colocalization of expanded ER, mitochondria, and DRP1 puncta during iron overload, an effect markedly reduced by PRDX5 overexpression. These results indicate that PRDX5 limits ROS-dependent ER–mitochondria coupling associated with aberrant mitochondrial fission. PRDX5 also preserved mitochondrial membrane potential and prevented cytochrome c release and caspase-3 cleavage, linking its redox-regulatory function to mitochondrial integrity and neuronal survival [35]. Importantly, this Ca^{2+}/calcineurin–DRP1 fission mechanism was also observed in vivo in PRDX5-deficient mice fed a high-iron diet. PRDX5 loss similarly exacerbated hippocampal iron accumulation, ER stress, and Ca^{2+}/calcineurin-mediated DRP1 dephosphorylation in vivo, producing CA3 subregion-specific neuronal loss and caspase-3 activation that were more pronounced in neurons than in glia and could be rescued by treatment with the ROS scavenger N-acetylcysteine [36]. Additionally, PRDX5 modulates mitochondrial dynamics in amyloid-β-associated neuronal stress. In HT-22 cells, PRDX5 overexpression reduced amyloid-β oligomer-induced ROS production and suppressed ERK–DRP1-dependent mitochondrial fragmentation and apoptosis [37]. Collectively, PRDX2 and PRDX5 regulate ER–mitochondria communication through distinct yet convergent mechanisms—redox-dependent control of mitochondrial

trafficking and Ca^{2+}-driven mitochondrial fission, respectively—with direct implications for mitochondrial quality control, as discussed below.

4.4. PRDX-Dependent Mitochondrial Quality Control and Neurodegeneration

ER stress-dependent regulation of mitochondrial quality control provides another potential mechanism by which PRDXs may influence neurodegeneration. In an MPP^+-induced cellular model and an MPTP-induced mouse model of PD, mitochondrial oxidative stress and ER stress were shown to be closely interconnected. MPP^+ increased mitochondrial ROS levels, mitochondrial Ca^{2+} accumulation, loss of ATP and mitochondrial membrane potential, and pronounced ER stress. The mitochondria-targeted antioxidant MitoQ attenuated this ER stress, supporting a reverse signaling pathway in which mitochondrial oxidative stress propagates back to disrupt ER proteostasis [5,68]. The study further identified Miro1 as a key link between ER stress and mitophagy. MPP^+-induced ER stress triggered accumulation of mitochondrial Miro1, which correlated with impaired PINK1/Parkin-dependent mitophagy. Pharmacological inhibition of ER stress with 4-phenylbutyric acid decreased Miro1 levels, restored PINK1 and Parkin signaling, reactivated mitophagic flux, lowered mitochondrial ROS, and preserved mitochondrial membrane potential. Genetic manipulation of Miro1 directly supported a functional relationship among ER stress, Miro1 accumulation, and defective mitochondrial turnover. Moreover, in vivo inhibition of ER stress protected dopaminergic neurons and ameliorated motor and cognitive deficits in MPTP-treated mice [9,68].

These observations are directly relevant to PRDX-mediated regulation of ER–mitochondria communication. PRDX2-dependent modulation of Armcx3 suggests that PRDX2 redox signaling may similarly influence mitochondrial positioning and MERC dynamics [25]. Concurrently, PRDX5-mediated suppression of ER stress, Ca^{2+} dysregulation, and calcineurin/ERK–DRP1 signaling may preserve mitochondrial morphology and support effective mitochondrial quality control [35,37]. Although a direct PRDX–Miro1–PINK1/Parkin signaling axis has not yet been established, these findings collectively suggest that PRDX-dependent suppression of oxidative stress and ER stress indirectly preserves mitophagy and mitochondrial turnover in neurodegenerative conditions.

4.5. PRDX-Dependent ER–Mitochondria Homeostasis in Neurodegenerative Diseases

The compartment-specific functions of PRDX2, PRDX3, PRDX4, and PRDX5 provide a framework for understanding how PRDX dysregulation may contribute to neurodegenerative disease. In AD, altered MERC function is associated with amyloidogenic processing, abnormal Ca^{2+} transfer, lipid metabolism, and mitochondrial dysfunction [65]. In this context, PRDX4 can suppress amyloid-β-induced ER oxidative stress and Ca^{2+} dysregulation, whereas PRDX3 and PRDX5 reduce mitochondrial oxidative stress and mitochondrial fragmentation, respectively [9,33,35,36]. These isoforms may thereby act at complementary checkpoints along the ER–mitochondria stress axis.

A similar relationship may operate in PD, in which α-synuclein and PINK1/Parkin-dependent mitochondrial quality control have been directly linked to altered MERC function, Ca^{2+} handling, and mitophagy [60,66], alongside additional PD-associated regulators of mitochondrial dynamics such as DJ-1, MFN2, and Miro. Mitochondrial PRDX5 protects neuronal cells against MPP^+-induced oxidative injury [34], and inhibition of ER stress independently rescues Miro1-dependent mitophagy and dopaminergic neuron survival in PD models [68]. Together, these findings indicate that maintaining ER and mitochondrial redox homeostasis may limit the downstream consequences of disrupted ER–mitochondria signaling.

In ALS, alterations in several PRDX isoforms have been reported in SOD1-mutant models [9]. PRDX6 is upregulated approximately four-fold in reactive astrocytes of paralyzed $SOD1^{G93A}$ mice, a response interpreted as a compensatory astrocytic defense against oxidative damage rather than a motor neuron-intrinsic protective mechanism [38]. Conversely, Schwann cell-secreted PRDX1 protects NSC-34 motor neurons from H_2O_2-induced death in vitro, and both PRDX1 mRNA in the lumbar spinal cord of $SOD1^{G93A}$ mice and PRDX1 secretion by Schwann cells expressing mutant SOD1 are reduced, suggesting that loss of this paracrine antioxidant support may also contribute to motor neuron death [69]. These isoform-level changes have not, however, been mechanistically linked to the TDP-43- and SOD1-driven MAM/MERC disruption described above [32,51], nor specifically to the VAPB–PTPIP51 tethering defect; whether altered PRDX6 or PRDX1 expression directly influences ER-mitochondria contact-site integrity in ALS motor neurons, or instead reflects a parallel, mechanistically separate oxidative-stress response, remains unknown. Resolving this specific gap—connecting isoform-level PRDX changes to MERC structural remodeling in ALS—represents a concrete, testable direction for future work.

Collectively, PRDXs may be viewed as organelle-specific redox checkpoints positioned on both sides of the ER–mitochondria interface. PRDX4 limits excessive peroxide accumulation and maintains proteostasis within the ER, whereas PRDX3 and PRDX5 constrain mitochondrial oxidative stress and preserve mitochondrial function. PRDX5 may additionally influence the functional coupling of these organelles by regulating ROS-dependent Ca^{2+} signaling and mitochondrial dynamics. When PRDX-mediated redox buffering capacity is insufficient due to downregulated expression, oxidative inactivation, or overwhelming ROS production, ER stress and mitochondrial dysfunction may reinforce each other. This reciprocal failure leads to mitochondrial Ca^{2+} overload, mitochondrial fragmentation, impaired quality control, and neuronal death. Consequently, restoring or selectively activating PRDX-dependent redox signaling pathways may be a strategy to interrupt the pathological ER–mitochondria stress cycle in neurodegenerative diseases (Table 1).

5. Pharmacological and Translational Implications of Targeting PRDXs

The compartment-specific neuroprotective effects of PRDX2–PRDX5 described above, together with the disease-associated loss-of-function phenotypes linked to reduced PRDX expression, indicate that restoring or augmenting PRDX activity is a mechanistically plausible therapeutic strategy across these disorders. Three broad pharmacological approaches have been explored to date: directly delivering or overexpressing a PRDX isoform, pharmacologically inducing endogenous PRDX expression through upstream transcriptional regulators, and pharmacologically reactivating the hyperoxidized, catalytically inactive pool of existing PRDX protein.

Direct gene delivery of PRDX3 has been tested as a therapeutic strategy in the $SOD1^{G93A}$ mouse model of ALS. Lentiviral PRDX3 overexpression increased survival by approximately 27% and reduced oxidative stress by approximately 42% in $SOD1^{G93A}$-expressing motor-neuron-like cells in vitro, and co-delivery of the transcription factor NRF2 produced comparable protection by inducing downstream antioxidant enzymes [29]. However, intramuscular AAV6-mediated delivery of PRDX3 or NRF2 in vivo transduced fewer than 5% of lumbar motor neurons and did not improve disease onset, progression, or survival in $SOD1^{G93A}$ mice, highlighting the need to optimize vector tropism, administration routes, and transduction efficiency to achieve therapeutically relevant PRDX expression in motor neurons [29].

Isoform-overexpression strategies targeting other PRDXs have shown more encouraging results in models of Parkinson's disease, whether tested in vivo or in dopa-minergic cell culture. Peptide-mediated striatal delivery of PRDX3 protected dopaminergic neu-

rons and improved motor and cognitive performance in a paraquat-induced mouse model of Parkinson's disease [39], and adenoviral overexpression of PRDX5 reduced paraquat-induced mitochondrial and cytoplasmic reactive oxygen species and cell death in SH-SY5Y dopaminergic cells in vitro [70]. Unlike the AAV6-mediated PRDX3/NRF2 delivery tested in the $SOD1^{G93A}$ ALS model above, both of these approaches relied on direct, localized striatal or intracellular delivery rather than peripheral, muscle-targeted injection. However, differences in disease models, PRDX isoforms, vector systems, and delivery routes may all contribute to the variable efficacy observed across these studies. Consistent with this isoform-overexpression strategy, PRDX4 overexpression has likewise been shown to protect HT-22 hippocampal neurons against amyloid-β oligomer- and glutamate-induced toxicity by limiting ER stress and intracellular Ca^{2+} overload [27,33], extending the therapeutic rationale for PRDX overexpression from the PRDX3- and PRDX5-based PD and ALS models discussed above to a PRDX4-based model relevant to AD. Together, these isoform-specific studies suggest that delivery route and target isoform, rather than PRDX overexpression per se, are likely to be key determinants of in vivo efficacy.

An alternative to direct PRDX gene delivery is pharmacological induction of endogenous PRDX expression through the Nrf2-antioxidant response element (ARE) pathway. In non-neuronal cell models, PRDX6 transcription is driven by an ARE in its promoter: Nrf2 activators increase PRDX6 expression through this element, whereas the Nrf2 repressor Keap1 suppresses it [71]. Because the Nrf2-ARE axis is already a validated target of several characterized small-molecule activators, these compounds offer a pharmacologically tractable, if currently indirect, route to boosting PRDX levels; whether they raise PRDX2-PRDX5 expression specifically at ER–mitochondria contact sites in neurons, as opposed to PRDX6 in the non-neuronal systems studied to date, has not been tested and would need to be established before this strategy could be considered for neurodegenerative disease. A third, mechanistically distinct strategy is the pharmacological preservation or reactivation of the existing PRDX pool rather than increasing its expression. Catalytically active 2-Cys PRDXs are prone to hyperoxidation of their peroxidatic cysteine to a sulfinic acid during periods of high peroxide flux, which inactivates the enzyme; this inactivation can be reversed by the ATP-dependent reductase sulfiredoxin, which is itself an Nrf2 target gene [72,73]. The Nrf2 activator 3H-1,2-dithiole-3-thione induces sulfiredoxin expression and measurably reduces PRDX hyperoxidation in cortical neurons, conferring protection against oxidative injury [72]. However, sulfiredoxin-mediated reactivation is restricted to the typical 2-Cys PRDXs (PRDX1-PRDX4) and does not act on the atypical 2-Cys PRDX5 or the 1-Cys PRDX6 [73], so this strategy would need to be paired with isoform-specific approaches to address PRDX5- or PRDX6-dependent pathology. As with the Nrf2–ARE-driven induction of PRDX6 transcription discussed above, Nrf2 activators should therefore be considered indirect modulators of PRDX function, with sulfiredoxin induction representing one potential mechanism through which PRDX peroxidase activity may be preserved.

Together, these early studies illustrate both the promise and the present limitations of PRDX-targeted therapeutics: isoform-specific overexpression has proven protective in vivo in Parkinson's disease models using direct, localized delivery, but the same general strategy has so far failed to improve outcomes in the SOD1G93A ALS model when delivered peripherally by AAV6; pharmacological induction via Nrf2-ARE activators remains to be tested in a neurodegeneration-relevant, PRDX2-PRDX5-expressing system; and sulfiredoxin-mediated reactivation of hyperoxidized PRDX has so far been characterized only for typical 2-Cys isoforms outside a neurodegeneration context. Clinically meaningful efficacy will likely depend on isoform selection, delivery route, cell-type-specific targeting, and confirmation that pharmacologically induced or reactivated PRDX reaches the relevant subcellu-

lar compartment; these considerations are revisited below in relation to disease-specific intervention strategies.

6. Conclusions and Future Perspective

Mitochondrial dysfunction and ER stress are now widely recognized as mechanistically coupled processes rather than independent contributors to neurodegeneration, with the ER–mitochondria contact site serving as the structural substrate for this coupling. This review organizes the PRDX literature around this interface, showing that PRDX2, PRDX3, PRDX4, and PRDX5 each intersect ER–mitochondria crosstalk at distinct molecular nodes. This framing distinguishes the present review from prior PRDX-focused surveys, which have typically organized the evidence by disease entity or by neuronal life-cycle stage rather than by the specific inter-organelle mechanisms through which PRDXs act.

Several gaps nonetheless remain. First, PRDX1 and PRDX6 have been little studied in the specific context of ER–mitochondria communication, and whether their predominantly cytosolic and lysosomal/membrane localizations preclude a direct role at MERCs remains unclear. Second, although several of the mechanisms reviewed here have since been confirmed in vivo, including in PRDX5-deficient mice and in toxin- or transgene-based mouse models of Parkinson's disease and ALS, much of the causal evidence still derives from neurotoxin- or peptide-induced cell culture models rather than from patient-derived neurons or human post-mortem tissue, so the extent to which these mechanisms operate in the intact, aging human nervous system remains to be established. Third, direct molecular links between PRDX-dependent redox signaling and core mitochondrial quality-control and MERC-tethering machinery remain to be established for several isoforms. These gaps point toward productive directions for future work. Structural and proximity-labeling approaches could help test whether PRDX isoforms physically associate with core tethering complexes rather than acting only through diffusible H_2O_2. Tissue- and cell-type-specific PRDX gain- or loss-of-function models, combined with in vivo MERC imaging, would help clarify whether protective effects observed in cell culture translate to disease-relevant contexts. Because PRDX overexpression was protective across the model systems reviewed here, PRDX-targeted therapeutic strategies represent a plausible avenue, though they will likely need to be tailored to the dominant PRDX deficit and organelle-stress signature of each disease. As detailed in Section 5, early isoform-specific overexpression and pharmacological induction strategies have shown encouraging protective effects in cellular and animal models of Parkinson's disease, whereas a comparable gene-therapy strategy has so far failed to improve outcomes in a peripherally delivered ALS model, underscoring that delivery route, isoform selection, and disease context will each shape translational success.

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