Endoplasmic Reticulum-Mitochondrial Cross-Talk in Neurodegenerative and Eye Diseases

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Abstract

Neurodegenerative diseases demonstrate the progressive decline of brain functions resulting in a significant deterioration in the quality of patient's life. With increasing life expectancy, there has been a significant increase in the incidence of these diseases. Neurodegenerative diseases like Alzheimer's, Parkinson's, and Amyotrophic lateral sclerosis are devastating and afflicts a large world population. Eye, given the similar neural and vascular similarity to the brain, demonstrates many pathological hallmarks of some of these neurological diseases. Moreover, these diseases create an economic and social burden to society. Despite tremendous efforts made in the drug discovery, there is no cure for these fatal diseases. Thus, there is an unmet need to understand cellular and molecular pathophysiology of these diseases. All these diseases demonstrate damage to a large number of seemingly disparate cellular processes and functions such as Ca^{+2} homeostasis, lipid metabolism, axonal transport, unfolded protein response, autophagy and inflammatory responses. Mitochondria are closely associated with Endoplasmic reticulum (ER) and ER-mitochondrial cross-talk regulates many of these cellular processes and functions damaged in neurodegenerative and eye diseases. Several studies have implicated the disruption of ER-mitochondria contacts in these diseases. This review is aimed at understanding and summarizing the role of ER-mitochondria interacting proteins in major neurodegenerative and eye diseases studied so far.

Keywords: Endoplasmic Reticulum; Mitochondria; ER-Mitochondrial Cross-Talk; Neurodegenerative Diseases; Eye Diseases

Abbreviations

ER: Endoplasmic Reticulum; MAMs: Mitochondria Associated ER Membranes; AD: Alzheimer's Disease; PD: Parkinson's Disease; ALS: Amyotrophic Lateral Sclerosis; FTD: Frontotemporal Dementia; APP: Amyloid Precursor Protein; PACS-2: Phosphofurin Acidic Cluster Sorting Protein-2; Mfn-2: Mitofusin-2; PINK1: PTEN-Induced Kinase 1; TDP-43: TAR DNA Binding Protein; VAPB: Vesicle-Associated Membrane Protein-Associated Protein B; PTPIP51: Protein Tyrosine Phosphatase-Interacting Protein-51, REEP1: Receptor Expression Enhancing Protein 1, HSP: Hereditary Spastic Paraplegia; EM: Electron Microscopy; SIM: Structure Illumination Microscopy, PALM: Photoactivation Localization Microscopy; STORM: Stochastic Optical Reconstruction Microscopy, AIF: Apoptosis-inducing Factor; AMD: Age-related Macular Degeneration; RPE: Retinal Pigmental Cells; HN: Humanin; ELP: Elastic-like Polypeptide; ERMES: ER-Mitochondria Encounter Structure; Mmm1: Maintenance of Mitochondrial Morphology Protein 1; PDZD8: PDZ Domain-Containing Protein 8; Bap3: B-Cell Receptor-Associated Protein 31; Fis1: Mitochondrial Fission Protein 1; VDAC: Voltage-Dependent Anion Channel; IP3R: Inositol 1,4,5-Triphosphatase Receptor; GRP75: Glucose-Regulated Protein 75

Introduction

In recent years, there has been tremendous interest in understanding the interactions between the endoplasmic reticulum (ER) and mitochondria or analyzing ER-mitochondria tethering proteins. ER and mitochondria are tubular organelles with an extensive network structure, which forms inter-organellar connections having a distance less than 30 nm. Moreover, mitochondria-associated ER membrane (MAM) interacts with mitochondria and is a major platform to regulate many physiological processes, including Ca^{+2} homeostasis [1-6], lipid synthesis and transfer [7,8], autophagosome formation [9], mitochondrial fragmentation [10] and apoptosis [11,12]. The abnormal-

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ity and disruption of ER-mitochondria interactions have been implicated in many neurodegenerative diseases [13-15]. Although the functional role of ER-mitochondrial cross-talk is widely accepted. However, the proteins involved in the cross-talk and its mechanisms of action remain elusive. Moreover, considering the complexity of the disease, targeting one branch of the ER stress pathway (Unfolded protein response) or mitochondria-mediated apoptotic pathway/mitochondrial stress might be insufficient for the therapeutic targets. Thus, understanding these diseases at the molecular level in different organelles such as ER and mitochondria or analyzing ER-mitochondria interactions with respect to disease's pathology can be one of the ways to refine the current pharmacological approaches.

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD) are few major devastating diseases that affect large world's population. 46 million people worldwide are affected by dementia associated with AD [16]. Moreover, there are above 7 million people living with PD [17]. ALS is a motor neuron disease and affects 400,000 people in the world [18] and also the second most common cause of presenile dementia after AD [19]. Together, these diseases not only cause suffering to patients and their families but also represent a massive economic burden to our societies as well. Despite these economic, social burdens and tremendous efforts made in the drug discovery, there is still no cure for these neurological diseases. Similar to brain, eye is an organ which mimics brain physiology and pathology [20,21]. Many early diagnostic and abnormal proteins in neurodegenerative diseases are expressed in the eye [22] and their functions have been implicated in the pathogenesis of both eye and brain diseases [23]. Therefore, it is essential to understand the disease pathogenesis in the brain and eye, which might complement each other and increase our understanding of the disease process.

ER-mitochondria Cross-talk in neurodegenerative diseases

In many neurodegenerative diseases including AD [24], PD [25-28] and ALS [29], ER-mitochondrial interactions are impaired.

Alzheimer's disease

AD affects approximately 46 million people across the world. For AD, there are two important proteins, Presenilin-1 (PS1) and Presenilin-2 (PS2), which are mutated in familial Alzheimer's [30]. These two proteins are a major component of the γ-secretase complex that processes Amyloid precursor protein (APP) to release β-Amyloid. The loss of these proteins or its mutation affects ER-mitochondrial interactions, which has also been confirmed in the AD mouse models [24,31,32] including APP transgenic mice [33]. Moreover, β-Amyloid and Presenilin are localized at MAM [30,34]. Specifically, expression of PS2, but not PS1 affects ER-mitochondrial associations in Mfn-2 (mitofusin-2) dependent manner [35]. Another protein called apolipoprotein E (ApoE4, encoded by ε4 alleles) regulates fat metabolism and increases the risk of Alzheimer's [36]. ApoE4 has been shown to upregulate the activity of proteins at MAM [37]. Two other MAM proteins, Phosphofurin acidic cluster sorting protein-2 (PACS-2) and sigmareceptors are essential for neural survival and elevated in the hippocampus for the mouse model of Alzheimer's disease [33]. In the same study, nanomolar concentrations of β-amyloid peptide increase many ER-mitochondria contact proteins as well as Ca^{+2} exchange [33]. However, the direct evidence of specific alteration in ER-mitochondria interaction was not clear in this study.
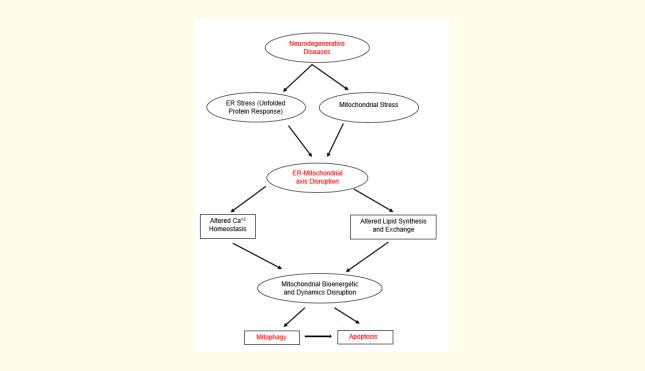
Parkinson's disease

Parkinson disease is another chronic neurological disorder affecting above 7 million people in the world. In Parkinson's disease, many proteins including PINK1 (PTEN-induced kinase 1), Parkin (encoded by PARK2 gene), protein deglycase DJ-1 and α-synuclein are mutated in different forms of the disease and alters ER-mitochondrial cross-talk [25-28]. PINK1 is a PD associated protein, controls mitochondria quality, and is often found at MAM. BECN1/Beclin1, a pro-autophagic protein is also found at MAM. Both PINK1 and Beclin1 enhances ER-Mitochondria interactions and autophagosome formation following mitophagy [38]. Miro, a well-characterized component of mitochondrial trafficking machinery regulates the effects of PINK1 for mitochondrial Ca^{+2} regulation and morphology [39]. DJ-1 is a protein deglycase, which restricts the aggregation of α-synuclein by its chaperone activity and functions as a redox-sensitive chaperone. DJ-1 overexpression promotes ER-mitochondria interactions. Similarly, point mutations of α-synuclein reduced ER-mitochondria interactions, decreased MAM protein functions and increased mitochondrial fragmentation [25,27]. Despite α-synuclein presence in MAM [25], its functional role with respect to ER-mitochondrial cross-talk is not clearly understood. Parkin (Parkinson juvenile disease protein 2) is an enzyme protein encoded by PARK2 gene, plays a prominent role in the ubiquitin-proteasome system and regulates protein breakdown. Parkin is upregulated during ER and mitochondrial stress and promotes ER-mitochondria interactions [40]. Moreover, parkin colocalizes with MAM proteins following excitotoxicity as well [41].

Amyotrophic lateral sclerosis

ALS is another major neurological disorder where different MAM proteins were implicated in its pathogenesis [42]. However, it is unclear whether upregulation or downregulation plays an important role in the pathogenesis of ALS. TAR DNA binding protein (TDP-43) is a major pathological protein in sporadic ALS, and, also a potential biomarker for ALS [42]. In ALS/FTD, TDP-43 protein is mutated and implicated in the disease pathogenesis [42]. Overexpression of wild-type and familial ALS/ FTD mutant TDP-43 reduced ER-mitochondria associations and disrupted Ca^{+2} exchange (mitochondrial Ca^{+2} exchange from ER) through activation of glycogen synthase kinase 3β (GSK3β) which disturbed VAPB-PTPIP51 interaction [29]. Vesicle-associated membrane protein-associated protein B (VAPB) is a MAM protein, which communicates with outer mitochondrial membrane protein called Protein tyrosine phosphatase-interacting protein-51 (PTPIP51) to form MAM tether complex [43]. Mutation in VAPB increases affinity for PTPIP51 and disrupts Ca^{+2} homeostasis [43]. The details of ER-mitochondria tether proteins are described below in a separate paragraph and, also in Table 1. Sigma 1 is another ER-associated chaperone protein implicated in ALS where the loss of its receptors contributes to some familial forms of ALS/FTD [44]. Moreover, Sigma 1 receptor disrupts ER-mitochondria associations in ALS [45]. Likewise, receptor expression enhancing protein 1 (REEP1) contributes to hereditary spastic paraplegia (HSP) and motor neuron disorders. REEP1 localizes to ER-mitochondria contact sites and affects ER-mitochondria associations [46]. HSP REEP1 disease mutants decrease ER-mitochondria interactions [46]. ALS causing superoxide dismutase 1 (SOD1) mutants also accumulates at MAM and disrupts MAM functions [47]. The overview of ER-mitochondrial cross-talk along with physiological relevance in neurodegenerative diseases is described in figure 1.

Figure 1: *Diagram showing the relationship between ER-mitochondrial axis disruption and apoptosis/mitophagy in neurodegenerative diseases. In neurodegenerative diseases, there is ER and mitochondrial stress which damages ER-Mitochondrial axis or alters the normal ER-mitochondrial interactions thereby changing the basic physiological functions of ER-mitochondrial axis leading to the disruption of mitochondrial bioenergetics and dynamics. This drives mitochondria towards mitophagy and ultimately cell towards apoptosis.*

Controversary

However, there are some controversies/inconsistencies in some of the findings related to proteins involved in ER-mitochondrial Cross-talk in AD and PD. In AD, one study demonstrated that ER-mitochondrial interactions are increased by the loss of familial Alzheimer's mutant Presenilin 1 [24]. However, another study suggested the loss of presenilin 2 but not presenilin 1 decreased ER-mitochondria

tethering proteins [31]. In PD, some study demonstrated that expression of wild-type and mutant PD α-synuclein decreased ER-mito-chondria associations, while others showed increased associations [25,27]. Moreover, there is also some discrepancy in parkin studies as well for PD. A recent study demonstrated increased ER-mitochondria tethering in primary fibroblasts from parkin knockout mice and PD patients with PARK2 gene mutations [48].

The reasons behind the differences in these findings are not clear. However, the most common method used to quantify ER-mitochon-dria contact sites is confocal microscopy and could be one of the major issues. ER-mitochondria contact sites are 10 - 30 nm distance apart, for which confocal microscopy is not an accurate technique for its quantification because it does not provide higher resolution as performed by Electron microscopy (EM) [11,49-51]. Also, the lateral resolution of the confocal microscope is about 250 nm, which is more than the required 10 - 30 nm distance of ER-mitochondria contact site. Another reason for the discrepancy in the findings for ER-mitochondria associations could be the different physiological response of ER and mitochondria in various neurodegenerative pro-cesses. For example, in some neurodegenerative diseases such as AD, mitochondria redistribute inside cells, which creates artifacts and interferes in quantifying ER-mitochondria contact sites. In some diseases, there is an induction of intracellular trafficking of mitochon-dria, which induces the accumulation of mitochondria in the perinuclear regions [51,52]. This phenomenon does not necessarily in-crease ER-mitochondria contact sites, which confocal microscope can't detect. The morphology of ER and mitochondria changes in many neurodegenerative processes, which doesn't imply changes in ER-mitochondria contact sites. The mechanisms behind these altered ER-mitochondria associations in these neurodegenerative diseases are still unknown. One reason could be the increased physiological demands of the cell under the diseased condition which might have upregulated ER-mitochondrial associations/ ER-mitochondria tether proteins.

Techniques to study ER-mitochondria interactions

EM is a powerful technique, but here also, it is important to quantify the proportion of mitochondria surface closely opposed to ER, instead of quantifying only the number of ER-mitochondria contact sites. Moreover, ER and mitochondria morphology changes in many neurodegenerative diseases, which doesn't imply changes in the ER-mitochondria contact sites. Other powerful instruments to quantify ER-mitochondria associations are Structure Illumination Microscopy (SIM), Photoactivation Localization Microscopy (PALM), Stochastic Optical Reconstruction Microscopy (STORM). SIM provides lateral resolution of 50 nm [53] whereas, STORM and PALM use single-molecule fluorescent localization method, which has a lateral resolution of 20 nm laterally [54] STORM also analyses ER-mitochondria associations in living cells [55]. Some other alternative to conventional microscopy is in situ ligation assays where fixed tissues are probed with primary antibodies to ER and MAM proteins, followed by secondary antibodies coupled to specific oligonucleotides [56]. Using labeled nucleotides facilitate microscopic detection and quantification of hybridization signals. In situ proximity, ligation assay has been successfully used for studying VAPB-PTPIP51 tethers [56]. Moreover, functional assays such as lipid metabolism, Ca^{+2} homeostasis will further support ER-mitochondria associations.

ER-mitochondrial cross-talk in the eye diseases

Eye reflects the changes observed in the brain during disease progression [20,23]. There has not been many studies investing the role of ER-mitochondrial cross-talk in eye diseases. However, there has been few eye diseases studied including Retinitis pigmentosa, Age-related macular degeneration (AMD). Retinitis pigmentosa is a blinding disease involving retinal degeneration, which results in the death of photoreceptors. In retinitis pigmentosa, apoptosis of photoreceptors results from the two apoptotic pathways, one from the mitochondria (Apoptosis-inducing factor, AIF) and other from the endoplasmic reticulum (Caspase-12). Both AIF and caspase-12 trans-locate to the nucleus and their translocation depends upon intracellular Ca^{+2} homeostasis and calpain activity [57]. Age-related macular degeneration (AMD) is the most common eye disease and a leading cause of blindness in older adults greater than 65 years in developed countries. Humanin, a mitochondrial-derived 21 - 24 amino acid peptide encoded within the mitochondrial DNA, is neuroprotective, anti-inflammatory, antiaging and antifibrinogenic in various cells and tissues [58]. In response to various ER stressors, (Tunicamycin, brefeldin A and Thapsigargin), humanin protects retinal pigmental cells (RPE) in a dose-dependent fashion. In these cells, ER stress also upregulated mitochondria superoxide and decreased mitochondria glutathione (GSH). Humanin restored GSH synthesis by elevating the catalytic subunit of the rate-limiting glutamylcysyeine ligase and inhibited superoxide production [59]. Moreover, Humanin is protective for RPE cells from oxidative stress, senescence and mitochondrial dysfunction [60]. It is not clear how Humanin protects ER-mediated

mitochondrial dysfunction. In the RPE, humanin is present both in ER and mitochondria [61]. It is unknown whether Humanin is found on the ER surface or inside the ER membrane. Moreover, oxidative stress induces mitochondrial dysfunction such as bioenergetics or DNA copy number, translocation of Bax, which is also rescued by humanin treatment [60]. Considering the multipotent effects of HN against ER and mitochondrial stress, HN analogs have been investigated and considered more potent than HN [58]. Furthermore, the effect of humanin on ER-mitochondrial cross-talk via calcium signaling is not unknown. HN has rapid tissue clearance rate resulting in less tissue availability and frequent administrations. Thus, a thermally responsive elastic-like polypeptide (ELP) fused with HN have been used in such cases [62].

ER-mitochondrial tethering complex

The most well studied ER-mitochondrial tethering complex is the yeast ER-mitochondria encounter structure (ERMES), composed of ER-membrane-bound maintenance of mitochondrial morphology protein 1 (Mmm1), the cytosolic linker mitochondrial distribution and morphology protein 12 (Mdm12), and the outer mitochondrial membrane protein Mdm34 and Mdm10. No functional ortholog has been found in multicellular organisms. PDZ domain-containing protein 8 (PDZD8) is a mammalian protein, which contains an SMP (Synaptotagmin-like mitochondrial-lipid binding protein) domain, which is synonymous with yeast ERMES proteins [27]. PDZD8 is localized at ER membranes in close contacts with mitochondria, mediates the tethering of ER and mitochondrial membranes and is critical for Ca^{+2} exchange between ER and mitochondria. Specifically, PDZD8 is required for ER-dependent mitochondrial Ca^{+2} mitochondrial calcium uptake [63]. Other important ER-mitochondrial tethering complex proteins have been described in Table 1.

ER-mitochondria tether protein complex	Functions
Mitofusin 2 (Mfn2)	GTPase implicated in the fusion of mitochondrial outer membrane, required for the juxtaposition of ER to mitochondria [64]. Regulates ER-Mitochondrial interactions/cross-talk in different tissues [64-66].
VAPB-PTPIP51 tether	Vesicle-associated membrane protein-associated protein B (VAPB) is an integral protein in ER responsible for unfolded protein response (UPR) and Ca^{+2} homeostasis [67]. VAPB interacts with Protein tyrosine phosphatase-interacting protein-51 (PTPIP51) which is an outer mitochondrial membrane protein [43]. Forms molecular scaffold to tether ER and mitochondria [29].
Fis1-Bap31 tether	B-cell receptor-associated protein 31 (Bap31) is an integral protein of ER, controls the fate of newly synthesized proteins and regulates Ca^{+2} homeostasis in ER [68]. Fis1 (Mitochondrial Fission protein 1) is an outer membrane mitochondrial protein. Fis1-Bap31 interaction forms important scaffold necessary for activation of caspase 8 and the initiation of apoptotic signals [69].
IP3r3-Grp75-VDAC1	Voltage-dependent anion channel (VDAC) is an outer mitochondrial protein and communicates with ER calcium-release channel inositol 1,4,5-triphosphatase receptor (IP3R) via chaperone glucose-regulated protein 75 (GRP75) [70,71]. May not have tethering role rather a MERC spacing/ filling function resulting from functionally coupling ER and mitochondrial in calcium exchanges.

***Table 1:** Summary of important of ER-mitochondria tether protein complex.*

Unanswered questions and future directions

a) In many neurodegenerative diseases, ER-mitochondria interactions are disrupted and contributes to disease pathogenesis. It needs to be investigated whether all or some neurodegenerative diseases cause damage to ER-mitochondria interactions/tether proteins.

b) All different neurodegenerative diseases involve accumulation or mutation of different protein types in affected neurons. However, these diseases affect similar cellular functions including altered Ca^{+2} metabolism, lipid metabolism, axonal transport, inflammatory responses. ER-mitochondria interface is the primary site for many of these biochemical processes and regulates them. This also suggests that disturbance in ER-mitochondria associations serve as a common convergent mechanism for neurodegeneration

since all basic biochemical processes are perturbed in these diseases. It is still to be determined whether all neurodegenerative diseases affect the ER-mitochondrial axis in a similar fashion or differently following the insults.

c) The mechanism behind the disruption of ER-mitochondrial axis in different neurodegenerative diseases remains unclear. For example, Is there a common or different mechanism for ER-mitochondrial axis damage for different neurodegenerative insults? Moreover, for therapy, which of ER-mitochondrial axis (most damaged or least damaged) should be considered given the effect could be different in various neurodegenerative diseases?

d) Studies are still underway to identify the complete set of proteins that directly connect ER and mitochondria i.e. ER-mitochondrial tether proteins. It is still unclear how ER-mitochondria tethers regulate ER-mitochondria interaction in different neurodegenerative diseases. Moreover, what proteins regulate the cross-talk between ER-mitochondria tethers during neurodegenerative processes?

e) It is yet to be determined whether disruption in ER-mitochondria contact sites/tethering proteins initiates the neurodegenerative processes or they represent secondary alterations that occur during the disease progression. Moving this forward, it will be critical to characterize ER-mitochondrial tethers, its pathophysiological role, and relevance and the mechanism of action on ER-mitochondrial contact sites under different neurodegenerative diseases.

f) There is an unmet need for devising new powerful techniques for the accurate quantification of ER-mitochondrial contact sites since this will aid in understanding the ER-mitochondrial axis after various kind of insults in neurodegenerative diseases. This will also help us reach on a consensus about the effect of different neurological diseases on ER-mitochondrial axis.

Conclusion

ER-mitochondrial cross-talk regulates many physiological processes and functions in the body. Specifically, ER-mitochondrial axis is an important platform for supporting various signalling pathways necessary for carrying out basic important cellular processes. Many studies have demonstrated that ER-mitochondrial interactions are altered in many neurological diseases and some eye diseases. However, it is unclear and still controversial how increase or decrease in ER-mitochondria interactions contributes to these various diseases. Understanding the role of ER-mitochondrial cross-talk will help explore many more ER or mitochondria related molecules useful for drug discovery in these diseases.

Funding

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