

## Review Article

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# ER stress in neurodegenerative disease: from disease mechanisms to therapeutic interventions

DOI 10.1515/ersc-2017-0002

Received March 13, 2017; accepted May 1, 2017

**Abstract:** The conception that protein aggregates composed by misfolded proteins underlies the occurrence of several neurodegenerative diseases suggests that this phenomenon may have a common origin, ultimately driven by disruption of proteostasis control. The unfolded protein response (UPR) embodies a major element of the proteostasis network, which is engaged by endoplasmic reticulum (ER) stress. Chronic ER stress may operate as a possible mechanism of neurodegeneration, contributing to synaptic alterations, neuroinflammation and neuronal loss. In this review we discuss most recent findings relating ER stress and the development of distinct neurodegenerative diseases, and the possible strategies for disease intervention.

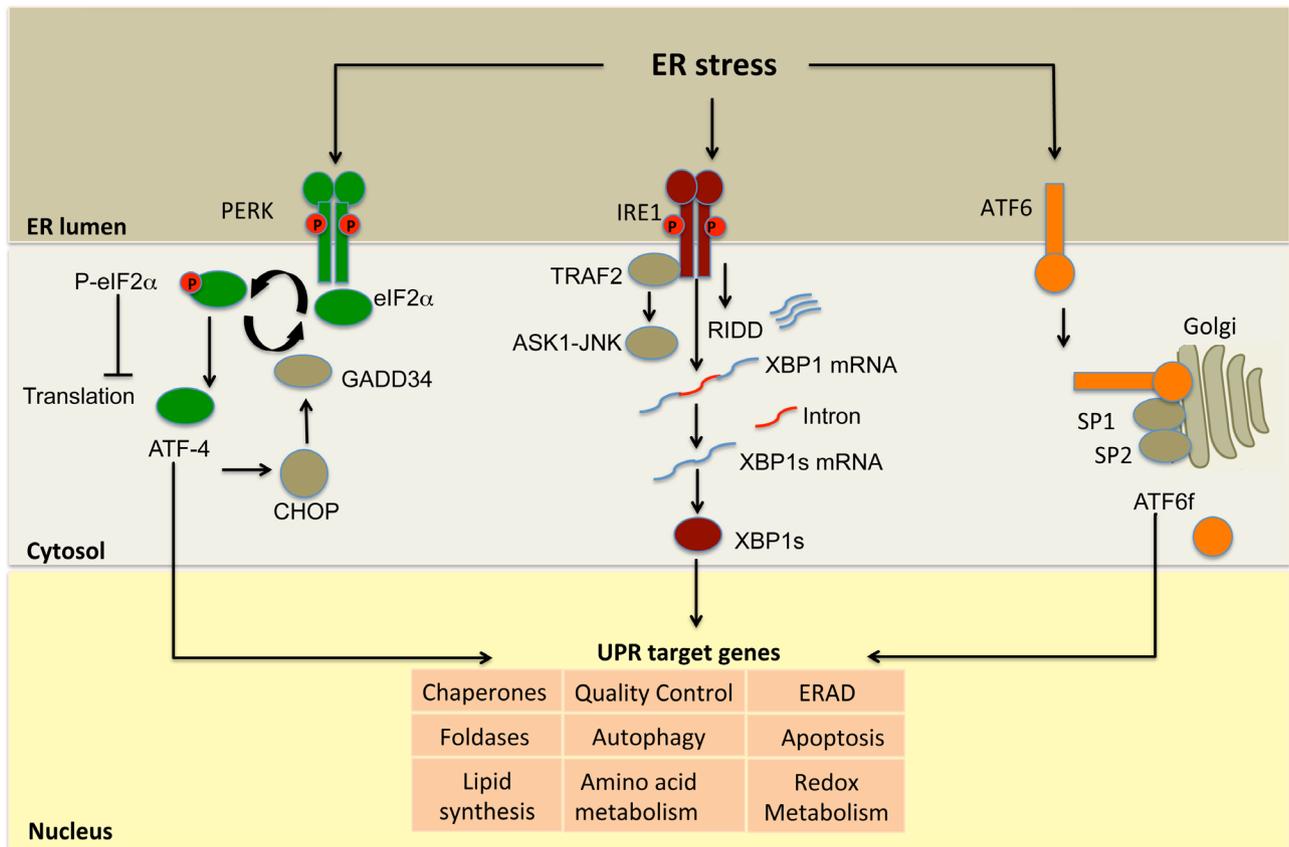
**Keywords:** Unfolded protein response, Neurodegeneration, Neurodegenerative Disease, ER stress, proteostasis

## 1 ER stress and the UPR

The endoplasmic reticulum (ER) is an organelle generating a reticular network involved in several functions including

protein folding, maturation, quality-control system, and secretion in addition to calcium storage and lipid synthesis [1,2]. Different harmful stimuli such as hypoxia, increased oxidation, glucose imbalance and disturbances in the normal function of the secretory pathway may lead to accumulation of unfolded or misfolded proteins at the ER lumen resulting in ER stress [3,4]. ER stress may in turn trigger the unfolded protein response (UPR), a well-conserved intracellular signalling pathway governed by the activation of three ER resident sensors: ATF6 (activating transcription factor 6), PERK [PKR (double-stranded-RNA-dependent protein kinase)-like ER kinase] and IRE1 $\alpha$  (inositol-requiring protein 1 $\alpha$ ), (Figure 1). Those three signalling branches activate distinct molecular pathways related to an increased capacity of protein folding, secretion, quality control and protein degradation [5,3]. Nevertheless, stressful stimuli that cannot be counterbalanced by the UPR may direct cell fate towards cell death by apoptosis [4, 3]. Activation of ATF6 enforces the transcription of genes related to protein folding and ER-associated degradation or ERAD [6]. PERK activation leads to increased phosphorylation of eukaryotic initiation factor-1 $\alpha$  (eIF2 $\alpha$ ), leading to a global protein synthesis shutdown. This event triggers the selective expression of activating transcription factor-4 (ATF4), which in turn upregulates the pro-apoptotic factor CHOP/GADD153 [7]. IRE1 $\alpha$  is an ER located RNase and kinase that represents the most conserved arm of UPR. Upon activation, IRE1 $\alpha$  catalyses the unconventional splicing of the mRNA encoding a potent transcription factor known as X-box binding protein 1 (XBP-1), leading to the expression of an active and stable protein termed XBP1s [8]. XBP1s acts as an important player in UPR signalling by upregulating the expression of chaperones, increasing the size of the ER and promoting the degradation of misfolded proteins through the ubiquitin proteasome system (UPS) by ERAD. In addition, through its RNase domain IRE1 can cleave several mRNAs regulating their stability through a process known as regulated IRE1-dependent decay (RIDD). Moreover, under sustained ER stress, IRE1 $\alpha$  may trigger cell death by the activation of JNK and the degradation of a subset of specific RNAs [9]. Overall, UPR mediates

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**Figure 1.** UPR signaling pathways in mammals. Accumulation of misfolded proteins in the ER activates the UPR sensors IRE1, ATF6 and PERK. Following ER stress, dimerization and autophosphorylation of IRE1 induces the splicing of mRNA encoding XBP1, leading to the expression of active transcription factor XBP1s thus upregulating ER chaperones, genes involved in the ERAD and genes regulating lipid synthesis. IRE1 also associates with TRAF2 inducing the activation of JNK and modulating autophagy and apoptosis. IRE1 endoribonuclease activity also induces a process known as regulated IRE1-dependent mRNA Decay (RIDD) that impacts different pathways including lipid biosynthesis and apoptosis. Upon ER stress, ATF6 is transported to the Golgi apparatus where it is cleaved by S1P and S2P (site 1 and 2 proteases), releasing the cytosolic ATF6 fragment (ATF6f) that functions as a transcription factor. ATF6f induces genes required for ERAD and modulates XBP1 mRNA levels. ER stress also activates PERK oligomerization and autophosphorylation leading to the phosphorylation of eIF2 $\alpha$ , which inhibits mRNA translation to the exception of the ATF4 mRNA. After translocation to the nucleus, ATF4 induces the expression of ER chaperones, genes related to autophagy, redox control and amino acid metabolism. ATF4 also controls genes related to apoptosis such as CHOP and GADD34.

a constant homeostatic surveillance of the proteome in highly secretory cells where the demand for high protein synthesis triggers physiological (non-apoptotic) levels of ER stress. However, chronic ER stress has emerged as an important driver of diverse diseases including cancer, diabetes, autoimmune diseases and neurodegenerative diseases [10,11].

## 2 UPR, protein aggregates and neurodegeneration – a complex interaction

The accumulation of protein aggregates correlates with disrupted function of synapses and neurodegeneration

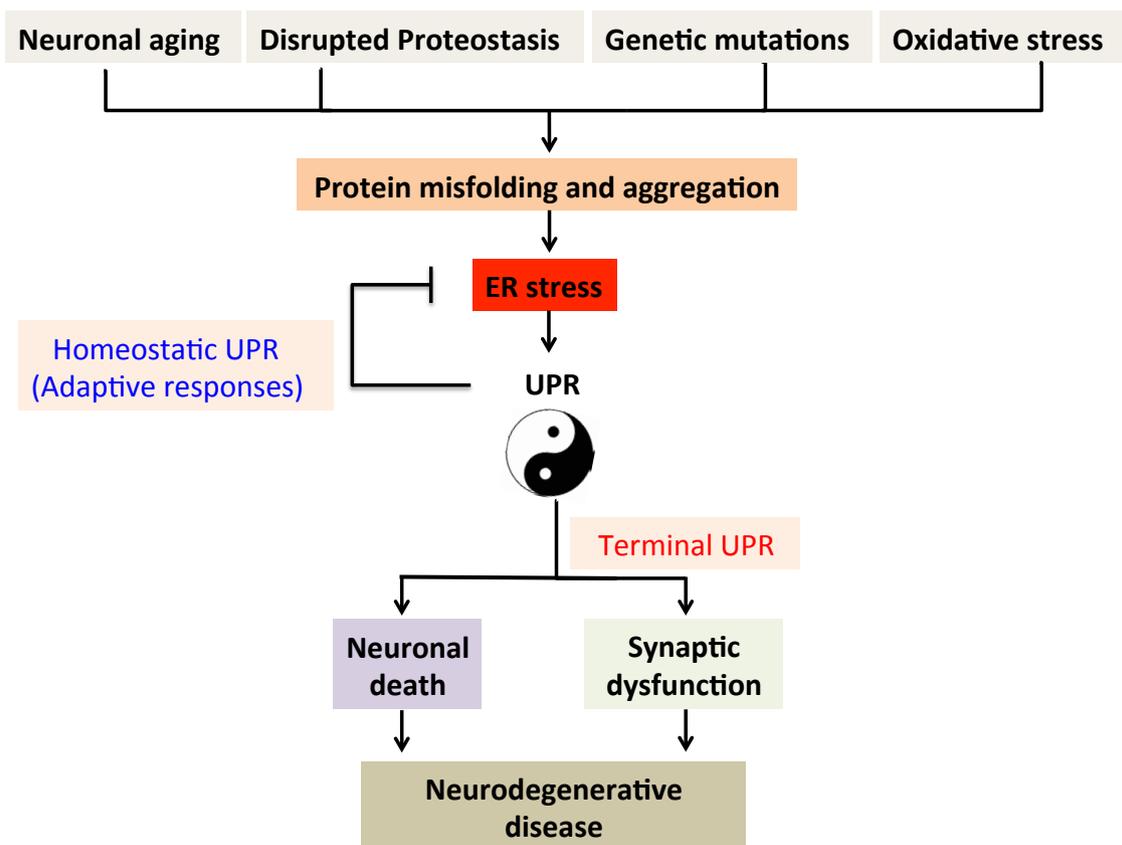
in distinct neurodegenerative diseases [5,12] and remarkably, protein aggregates are also present in the brain of subjects suffering from acute deleterious conditions such as brain ischemia [13,14]. Protein misfolding disorders (PMDs) include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), prion-related disorders (PrDs), among others [15] and different PMDs are marked by distinct misfolded protein aggregates that arise in divergent brain regions inducing synaptic dysfunction and degeneration in vulnerable neuronal populations [16].

Accumulating evidence suggests that UPR mediators are directly involved with the pathophysiology of PMDs although their role in the modulation of synaptic and

neuronal physiology in such conditions remains elusive [5]. Accordingly, the presence of ER stress markers have been described in patient samples with AD [17,18], PD [19], HD [20], ALS [21], and Prion diseases [22] and ER stress markers often co-localize with protein aggregates in the brain of patients [1,5,23-25]. Those findings could be interpreted as (i) neuroprotective signals to sustain proteostasis, (ii) a pro-degenerative stimuli due to chronic ER dysfunction or (iii) an epiphenomenon that is irrelevant to the disease process (Figure 2). In the next sections we will discuss the involvement of the UPR in different PMDs highlighting its implication to synaptic dysfunction and neuronal degeneration. In this review we aim to discuss most recent findings relating PMDs and ER stress in addition to speculate about how the UPR may regulate the physiopathology and outcomes of neurodegenerative diseases, thus shedding light into such complex causality.

### 3 Alzheimer's disease

AD represents one of the biggest disease-related burdens for modern society with an estimated health-care cost of USD\$172 billion per year only in USA [26, 27]. Its symptoms are characterized by a progressive and irreversible degeneration of the brain that leads to a gradual memory loss and decline of cognition and eventual death [27]. Analysis of patient brains led to the identification of AD histopathological markers, namely, senile plaques (also known as amyloid plaques) and neurofibrillary tangles composed respectively by misfolded amyloid  $\beta$  protein aggregates and hyperphosphorylated Tau (p-Tau) [28,29]. Disturbances in amyloid  $\beta$  processing leads to the accumulation of neurotoxic oligomers that forms intra and extracellular deposits, which account for disruption of synaptic transmission and neuronal survival hence leading to the devastating symptoms associated to the disease [30,31].



**Figure 2.** UPR signaling outputs and neurodegeneration. Distinct stimuli or genetic mutations may induce the misfolding of an underlying protein, generating different types of aggregates ranging from small oligomeric species to inclusion bodies thus leading to ER stress, engaging the activation of UPR. Early homeostatic UPR responses are triggered in order to resolve ER stress hence restoring ER function and maintaining cell survival. Unresolved ER stress leads to sustained activation of UPR leading to apoptosis to eliminate irreversibly damaged cells. Additionally, chronic ER stress may also affect synaptic function by repressing protein translation. Overall, UPR activation stands as an expressive driving force in the pathogenesis of neurodegenerative disease.

Mutations in presenilin-1, a gene related to an increased incidence of familial AD, was shown to downregulate BiP [32] thus suggesting that presenilin mutations were capable of altering the UPR firing and ER homeostasis, although opposite results showed that neither loss of presenilin-1 nor expression of its variants is sufficient to trigger UPR [33]. Upregulation of ER chaperones, including heat shock protein-27 (HSP-27) and BiP/GRP78, were observed in the brain of AD patients [34] and BiP presented increased expression in neurons that did not show deterioration, suggesting that it may exert a neuroprotective role prior to degeneration in AD. Patients in different Braak stages show up-regulation of BiP in the temporal cortex and hippocampus of AD patients that positively correlates with increased neurofibrillary tangles and amyloid pathology [17] and neurons positive for BiP did not co-localize with neurofibrillary tangles, suggesting that BiP expression preceded tangle formation. Similarly, the expression of the disulphide isomerase (PDI) was also shown to co-localize with neurofibrillary tangles in AD patients brain [49].

The PERK-eIF2 $\alpha$  pathway is another arm of UPR with important implications for AD [35]. Hippocampal neurons from AD patients exhibited an increased expression of phospho-PERK when compared to non-demented controls [36], which positively correlated with Braak stage. Those findings are also consistent with animal models for AD [37, 38] and Tau was shown to interfere with ER-associated degradation (ERAD). In addition, eIF2 $\alpha$  phosphorylation modulates BACE-1 expression in AD mice [39]. ATF4 was also shown to regulate gamma-secretase activity during amino acid imbalance, which triggers ER stress, also favouring amyloidogenic pathway [40]. Neuronal cultures treated with amyloid  $\beta$  show increased phosphorylation of PERK, which confers cellular protection, as its silencing increases neuronal death following amyloid  $\beta$  treatment [41]. Therefore, it is possible that the UPR is activated to sustain neuronal homeostasis and prevent neurodegeneration linked with AD. AD patients often have neurons containing neurofibrillary tangles that colocalizes with phosphorylated eIF2 $\alpha$  and PERK [56] which is also described in the hippocampus of aged P301L mutant Tau transgenic mice [57]. Accordingly, ERAD machinery is disrupted by Tau accumulation leading to ER stress [37]. Nevertheless, a recent report described that treatment with both chemical chaperone TUDCA (a treatment known to attenuate ER stress) or a specific small-molecule inhibitor of the PERK pathway prevents phosphorylation of Tau mediated by metabolic stress [58]. Of note, phosphorylation of Tau is sufficient to activate UPR and pharmacological-induction of ER stress may as

well induce phosphorylation of Tau [57] suggesting that UPR and tau hyperphosphorylation may create a positive feedback loop, thus forming a vicious cycle of neuronal degeneration signalling. Importantly, targeting deletion of PERK expression in the context of AD restored synaptic function due to the recovery of protein synthesis of synaptic proteins, improving memory capacity and synaptic transmission [52,53]. Similarly, ablating the expression of other eIF2 $\alpha$  kinases like PKR and GCN-2 impact synaptic function in AD models [54,52]. ATF4 expression was also recently shown to control axonal degeneration in AD models through a cell-nonautonomous mechanism [55]. Thus, exacerbated PERK signalling may have detrimental effects that enhance neurodegeneration and synaptic dysfunction through different mechanisms of action.

IRE1-XBP1 is another UPR branch implicated with AD pathophysiology. We recently demonstrated that in human post-mortem tissue IRE1 activation progresses as the disease evolves. Using genetic manipulation of IRE1 in the nervous system, we determined the functional significance of IRE1 to AD, demonstrating that ablation of its expression reduces amyloid plaque load and improves synaptic and cognitive function [43]. XBP1 is one of the main downstream components of IRE1 mediating proteostasis adjustment, promoting cell survival. In agreement with this concept, expression of active XBP1s in transgenic flies expressing amyloid  $\beta$  prevented neuronal loss [44]. Consistent with this, brain samples from AD patients presented augmented XBP1 [41]. XBP1 mRNA splicing is also observed after amyloid  $\beta$  treatment in neuronal cell lines [45] and in the temporal cortex of AD patients [43, 46]. Remarkably, genome wide screening to identify XBP1s-target genes uncovered a cluster of genes related to AD [47] and an etiological genetic association between XBP1 promoter polymorphism and AD increased risk development was revealed in the Chinese population [48]. Consistent with this we recently reported that XBP1 expression directly impacts APP metabolism [43]. A recent study indicated that delivering the active form of XBP1 into the hippocampus of AD mice restored synaptic function [50]. This is in agreement with recent findings indicating that XBP1s expression has a relevant role in controlling learning and memory-related processes [51]. Moreover, overexpression of XBP1s in fly models that overexpress Tau presented relevant protective effects [59]. Finally, IRE1 may trigger JNK-3 in the brain following amyloid  $\beta$  exposure in animal models and its deletion restores the translational block induced by oligomeric amyloid  $\beta$  and effect of UPR [42]. Taken together, cumulative evidence suggests the existence of a complex regulatory molecular network that mediates AD pathology by the ER stress response although

the number of studies that directly manipulate the UPR in AD models remains erratic [18]. Such approaches will certainly shed light into its complicated relation in order to better establish a solid impact of UPR in AD pathogenesis.

## 4 Parkinson's disease

PD is characterized by severe motor dysfunction composed by rest tremor, slowness of movement, rigidity and postural instability [60]. Like AD, its physiopathology is marked by the presence of neurofibrillary deposits of misfolded proteins known as Lewy bodies composed by misfolded protein  $\alpha$ -synuclein which colocalize with ubiquitin [61]. Despite most cases of PD cases are sporadic, mutations in several genes including SNCA, LRRK2, PRKN, DJ1, PINK1, and ATP13A2 trigger familial parkinsonian syndromes which account for less than 10% of the total PD cases [62] and mutations in leucine-rich repeat serine/threonine kinase 2 gene (LRRK2/PARK8) occur in 1-2% of genetic cases, being the most frequent cause of familial PD [61].

Drugs that elicit specific neuronal death for dopaminergic neurons such as 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-pyridinium (MPP+), and rotenone have been implemented in order to understand the molecular pathways responsible for neuronal degeneration in PD [63,64]. PC12 cells exposed to 6-hydroxydopamine presented an increased expression of transcripts associated with the UPR, sustaining that ER stress mediators may regulate neuronal death associated to PD [64]. Those results were confirmed by the observation of augmented phosphorylation of IRE1 and PERK besides an increased expression of its downstream targets in that model which are also present in post mortem tissue from PD patients [65]. Increased phosphorylation of PERK and eIF2 $\alpha$  was in co-localization with  $\alpha$ -synuclein inclusions was reported in the substantia nigra of PD patients. Other studies were also able to identify other ER stress markers in brain tissue from PD patients such as PDI [66] and components of ERAD like Herp [67] in co-localization with Lewy bodies and recently tunicamycin was shown to induce  $\alpha$ -synuclein oligomerization *in vivo* [68].

Genetic models of PD that include transgenic mice overexpressing various human variants of  $\alpha$ -synuclein in the brain also point to UPR triggering as a molecular target of neuronal degeneration [69]. Consistently,  $\alpha$ -synucleinopathy in mice is coincident with induction of ER stress and leads to abnormal UPR signal, thus leading to cell death pathway activation and a fraction of monomers and aggregates of  $\alpha$ -synuclein locates inside the ER, where it is found in association with ER chaperones

[70,71]. Remarkably, treating mutant A53T mice with salubrinal attenuated the onset of motor dysfunction, although this treatment was not sufficient to protect dopaminergic neurons following adeno-associated (AAV) distribution of  $\alpha$ -Synuclein mutant A53T in rats [72]. Other UPR mediators that were shown to be upregulated in the brain of  $\alpha$ -synuclein transgenic mice also include BiP, XBP1, CHOP, and ATF4 [72-74]. Interestingly, ER stress induction after tunicamycin treatment was sufficient to increase  $\alpha$ -synuclein aggregation, indicating a causal relation in disease pathogenesis and also sustaining that UPR dysfunction may act as a positive feedback for aggregation and cellular death [75]. Using screening system in yeast, the Lindquist lab demonstrated that  $\alpha$ -synuclein directly targets and inhibits vesicular trafficking from ER to Golgi apparatus by interacting with RAB1 [76]. Overexpression of RAB1 protected against  $\alpha$ -synuclein toxicity on a fly model and also attenuated motor deficits in a rat model [77]. Remarkably, human dopaminergic neurons generated from pluripotent stem (iPS) cells from Parkinson patients harbouring  $\alpha$ -synuclein mutations validated the importance of ER stress in the disease process [78]. Finally,  $\alpha$ -synuclein was shown to disrupt OPII ER-Golgi transport, a pathway crucial for activation and signalling by ATF6 [79] as  $\alpha$ -synuclein inhibits the processing of ATF6 both in a direct and indirect manner hence decreasing ERAD function.

LRRK2 is the most relevant gene mutated in PD. The pathogenesis of LRRK2 has been also linked to ER stress as it partially localizes in the ER in dopaminergic neurons of PD patients [80]. Using *C. elegans*, it was shown that LRRK2 confers protection to dopaminergic neurons against 6-OHDA treatment or human  $\alpha$ -synuclein expression, a phenomena associated with increased expression of the ER chaperone BiP [81]. Additionally, *C. elegans* lacking LRRK-2 homolog are more susceptible to ER stress [82]. Other important gene linked to familial PD that has been reported to alter ER function is E3 ubiquitin ligase Parkin/PARK2, related to the ubiquitin proteasome system (UPS) and to ERAD (19). Parkin was shown to be transcriptionally regulated by ATF4, thus suggesting that it acts as a ER stress-inducible protein that mediate cytoprotective mechanisms [83] and its subcellular distribution is altered following ER stress [84]. Of interest, Parkin-associated endothelin-receptor like receptor (Pael-R), a target for Parkin-dependent degradation by the proteasome, was shown to induce UPR triggering thus leading to neuronal death, a condition that were worsened by ER chaperone dysfunction [85].

Genetic manipulation of UPR was shown to regulate dopaminergic neuronal death in PD models.

Unexpectedly, genetic ablation of XBP1 throughout brain development increased neuronal resistance following 6-OHDA treatment, which was accompanied by the up-regulation of several UPR effectors in the substantia nigra, while there was no activation of pro-apoptotic UPR markers such as CHOP [86]. The concept of *hormesis* was proposed as the occurrence of mild ER stress may engage a protective program [1,87]. In agreement with this, treatment with non-lethal doses of tunicamycin in flies and mice models of PD provided protection against neurodegeneration [88]. Gene therapy to deliver XBP1 into the substantia nigra of adult animals protected against neurodegeneration induced by PD-inducing neurotoxins [86,89]. This observation was also confirmed in a model where XBP1 is delivered to neuronal stem cells transferred to animals treated with rotenone [90]. ATF6 deficient animals exhibit increased ubiquitin positive inclusions and exacerbated dopaminergic neuron loss following MPTP treatment [91,92]. Overexpression of BiP using a gene therapy strategy also proved to be neuroprotective for dopaminergic neurons after overexpression of human  $\alpha$ -synuclein in rats [93]. Finally, genetic ablation of pro-apoptotic CHOP/GADD153 has also been shown to be beneficial for dopaminergic neuronal survival following 6-OHDA but not after MPTP treatment, sustaining that UPR contribution in distinct PD models may be highly influenced by the chosen toxin for dopaminergic degeneration [7].

Taken together, ER stress has a pivotal role in the regulation of dopaminergic neuron survival and physiology thus representing an interesting target for disease intervention [19]. However, caution must be taken with interpretation as different models for PD may elicit different UPR components recruitment and the final output of manipulating the UPR may lead to contrasting results in a context dependent manner.

## 5 Amyotrophic lateral sclerosis

ALS is an adult-onset fatal neurodegenerative disease marked by the progressive degeneration of upper and lower motor neurons, in brainstem, cortex and spinal cord leading to paralysis and muscle atrophy, standing as the most common motoneuron disease [94]. The etiology of sporadic ALS, which account for nearly 90% of cases is not well defined but inherited genetic defects in distinct genes have been linked to familial cases of ALS [95]. Approximately 20% of familial cases, and 1–2% of all ALS cases, are caused by mutations in the gene encoding superoxide dismutase-1 (SOD1) [95] and now nearly 140

different ALS-linked SOD1 mutations have been identified [96]. Mutated genes implicated in familial ALS also include TAR DNA-binding protein 43 (TDP-43), FUS, ubiquilin-2 and C9ORF72; which are all linked to alterations to mRNA metabolism and proteostasis [94].

ALS is a disease where the involvement of ER stress is well defined and validated by several groups using different disease models. Importantly, ER stress has been proposed as one of the earliest molecular defects underlying the differential neuronal vulnerability observed [21]. Both ALS patients and mutant SOD1 mice present alterations in ER morphology as patients exhibit fragmentation of the rough ER, irregular distension of the rER cisternae and a detachment of ribosomes in degenerating anterior horn cells [97,98]. Accordingly, ER stress triggering was shown in post-mortem tissue by the presence of UPR markers BiP, calnexin and PDI in co-localization with mutant SOD1 [99-101]. Moreover, expression of XBP1 and ATF4 has been shown in human postmortem spinal cord tissue from sALS cases [102]. Remarkably, three distinct mouse models for ALS shows that ER stress specifically occurs in vulnerable motoneurons before any denervation is observed, which is followed by selective axonal degeneration [103]. In the same line, two proteomic screenings of spinal cord from mutant SOD1 mice revealed significant up-regulation of chaperone PDI and ERp57 [101, 104]. Moreover, PDI was found in co-localization with TDP-43 and SOD1 in swollen neurites and neuronal cytoplasmic inclusion of patients with ALS [105] and single nucleotide polymorphisms (SNPs) in intronic regions of the PDIA1 gene were shown to act as risk factors for ALS [106]. Of interest, our group recently identified mutations both in PDIA1 and ERp57 as risk factors to develop ALS and demonstrated a functional effect on the maintenance of neuromuscular junctions [107, 108].

Studies in animal models indicated that PDI mutations triggers motor defects associated with a disruption of motoneuron connectivity [104]. Similarly, calreticulin decrease in ALS mice, which accelerates early-stage muscle weakness and muscle denervation [109]. Additionally, mutant mice for BiP develop spontaneous motor disease during aging, associated with selective motoneuron degeneration and aggregation of wild-type endogenous SOD1 [110]. Finally, expression of the BiP co-factor SIL1 was recently reported to underlay in part the differential motoneuron vulnerability in ALS and gene therapy to deliver SIL1 to the nervous system has outstanding protective effects against experimental ALS [111]. Thus, alterations on the ER folding capacity may be part of the etiology of the disease. In addition to increase BiP and PDI expression [112], mutant SOD1 expression triggers chronic

PERK signaling [101,103,113] and the presence of CHOP/GADD153 was confirmed both in spinal cords of sporadic ALS patients and ALS transgenic mice [114]. A ribosome profiling analysis *in vivo* of motoneurons revealed that chronic ER stress is a major pathological signature in this ALS model [115]. Similarly, gene expression analysis of ALS brain tissue from patients carrying C9orf72 mutations, the most relevant genetic alteration in ALS, mutations shows major alteration in ER stress-related genes in cerebellum [116]. In agreement with this, expression of RAN peptides derived from C9orf72 mutation in cell culture also triggers abnormal levels of ER stress [117].

Moreover, eIF2 $\alpha$  phosphorylation is upregulated by TDP-43 overexpression in flies and its pharmacological inhibition was sufficient to attenuate its toxicity [118]; additionally, targeting one copy of PERK accelerated the disease process [119]. Based on all these evidence therapeutic strategies to target eIF2 $\alpha$  phosphorylation have been tested using pharmacological approaches. Accordingly, salubrial treatment in three different mice models for ALS delayed disease progression [103] although another publication has indicated that guanabenz treatment (a specific inhibitor of the ER stress inducible eIF2 $\alpha$  phosphatase) accelerated ALS pathogenesis [120], whereas others observed protection following guanabenz treatment [121, 122]. Remarkably, another new small molecule termed Sephin-1 (a derivate of guanabenz), showed almost full protection in mutant SOD1 mice [123]. Our group presented evidence indicating that ATF4 expression modulates ALS pathogenesis [124]. Deletion of the ATF4 gene was sufficient to increase lifespan in mutant SOD1 mice, reducing expression of pro-apoptotic genes BIM and CHOP [124]. However, unexpectedly, ATF4 deletion increased SOD1 aggregation both *in vivo* and *in vitro* thus confirming its importance in ALS physiopathology [124]. Interestingly, CHOP increased expression was shown both in neurons and astrocytes, oligodendrocytes and microglia, supporting the theory that UPR glial modulation might also regulate ALS physiopathology [125].

The contribution of XBP1 to ALS has also been tested using animal models and provided interesting concepts. Using a mutant SOD1 transgenic mouse with deletion of XBP1 specifically in the nervous system, our group has unexpectedly found that XBP1 ablation could decrease the severity of experimental ALS thus increasing lifespan [102]. This phenotype correlated with increased macroautophagy machinery activation in motoneurons in the absence of XBP1. Whether direct manipulation of IRE1-XBP1s axis may prove efficient into ALS pathogenesis ablation is still an open question in literature [21]. Finally,

a novel autosomal-dominant ALS-causative gene was identified in 2004, which encodes the vesicle-associated membrane protein-associated protein B (VAPB) [126]. Interestingly, this protein was shown to interact with ATF6 via its cytosolic domain and its malfunction could disrupt its activity [127]. Authors sustain that such malfunction may contribute to the pathological mechanisms of degenerative motor neuron disease. Similarly, transgenic mice for ALS-linked mutant VAPB show signs of ER stress [128]. Taken together, the ALS field has witness great advances in experimental strategies with therapeutic potential based on UPR for the future.

## 6 Huntington's disease

HD is an autosomal-dominant, progressive neurodegenerative disease with symptoms that include chorea and dystonia, incoordination, cognitive decline, and behavioural difficulties [129]. HD is caused by a mutation in the first exon of the Huntingtin (HTT) gene, which contains a tract of glutamine residues (polyQ repeats) that can vary in length amongst individuals resulting in a mutated protein HTT with an expanded CAG repeat [20] that are believed to exert a toxic gain of function [127,128]. Accordingly, polyQ expansions in different proteins are directly related to the pathology of at least nine different neurodegenerative disorders, including HD; one of each represented by a different subset of vulnerable neuronal populations [131]. Expression of mutant HTT and aggregate formation in cytosol and nucleus are believed to overcome the proteostasis machinery, thus altering cell normal physiology [20]. Mutant HTT may disrupt different cellular pathways related to protein turnover [132], transport [131] and the UPS [132, 130] in addition to induce ER stress in cellular models [9,135,136]. One event particularly disturbed by poly(Q) expanded repeats is ERAD, leading to ER stress [133, 135].

UPR downstream targets BiP, HERP and CHOP were shown to be upregulated in brain samples from HD patients [138] which is also observed in an animal model for HD [139]. A recent study performed a bioinformatic analyses that assembled different sets of genes associated with the UPR and examined whether the included genes show differential expression in HD models and patients. This report identified a complex network of genes that provide a potential link between UPR and HD and its relation to neurodegeneration [130]. Our group demonstrated that ablating XBP1 expression in the full-length mutant HTT transgenic mice is sufficient to reduce neuronal loss in the striatum in addition to improve motor performance [8].

These protective effects were in line with decreased HTT accumulation mediated by the induction of autophagy, possibly involving the upregulation of Forkhead box O1 (FoxO1) [8]. In contrast, ATF4 deficiency did not affect mutant HTT aggregation [8]. As autophagy is suggested to be the preferential degradation pathway for misfolded protein aggregates, including those formed as part of mutant HTT [20] and is proposed to fail in the disease process [140], XBP1 may stand as a central mediator of HTT clearance in HD pathogenesis. Accordingly, delivering AAV-XBP1 to the striatum of adult mice overexpressing a mutant HTT reduced its accumulation [141]. Another recent report suggested that ATF6 might be neuroprotective in models of HD [142]. Overall, different methodological approaches have indicated that the alterations in the secretory pathway observed in HD may be linked to perturbations at the level of ERAD/protein quality control mechanisms, ER/Golgi trafficking, endocytosis, vesicular trafficking, ER calcium homeostasis and autophagy/lysosomal-mediated protein degradation, thus resulting on ER stress as a common feature [143].

In agreement with the observations obtained with XBP1 deficient animals, cell-based functional screening using a mutant HTT aggregation assay identified IRE1 as a potential inducer of its aggregation [144]. Other studies suggest that PERK signalling may also influence mutant HTT biology as eIF2 $\alpha$  phosphorylation was shown as a crucial step for autophagy induction mediated by HTT aggregates [145]. In general, HD is the disease where ER stress has been less explored and functional data is still missing.

## 7 Prion-related disorders

PrDs, also known as transmissible spongiform encephalopathies, are a group of diseases characterized by rapid neurological dysfunction that may include dementia, ataxia and psychiatric disturbances. Its etiology is divided into infectious (derived from the exposure to material contaminated with infectious prions), sporadic (spontaneous origin) or familial (inherited in an autosomal dominant manner) PrDs. Human familial PrDs include some forms of Creutzfeldt-Jacob disease (CJD), Gertmann-Straussler-Sheinker syndrome and fatal familial insomnia [146]. The main molecular event in the pathogenesis of prion diseases is the conversion of the normal cellular prion protein (termed PrP<sup>C</sup>) into the pathological form denoted PrP<sup>Sc</sup> (for scrapie associated PrP) [147]. The possible involvement of ER stress in PrDs was initially highlighted by the finding of the upregulation

of the ER chaperones Grp78/BiP, Grp94 and Grp58/ERp57 in the cortex of patients affected with variant CJD and sporadic CJD [148]. Accordingly, ERp57 was reported as the major hit of a proteomic screening in the cerebellum of humans patients affected with sporadic CJD [149]. Mice infected with scrapie prions presents a profile of expression in the hippocampus revealing that most genes affected by prion infection are related with mediators of ER stress [150]. However, other studies in CJD have not found signs of ER stress [151]. Interestingly, mice infected with scrapie prions show markers of ER stress during the pre-symptomatic phase of the disease following PrP<sup>Sc</sup> accumulation, including high levels of the disulfide isomerase Grp58/ERp57 expression and also Grp78 and Grp94 increased expression during the symptomatic phase [152]. Remarkably, in the same model, neuronal loss is prominent only at the late stage of the disease, which correlates with increased pro-caspase-12 processing and decreased ERp57 expression [148] although knock outs for caspase-12 shows no alteration in disease progression [153]. ERp57/Grp58 has a neuroprotective role in PrDs as demonstrated in cellular and animal models [152] and ERp57 is also relevant for the synthesis and folding of PrP [154]. Exposure of cells to purified PrP<sup>Sc</sup> extracted from the brain of scrapie-infected mice results in ER stress. Remarkably, targeting of the anti-apoptotic protein BCL-2 to the ER membrane could decrease PrP<sup>Sc</sup> toxicity and cells infected with prions were more susceptible to ER stress-induced apoptosis [148, 155, 156]. At the molecular level PrP<sup>Sc</sup> conversion may affect ER calcium homeostasis [157, 155], triggering ER stress [154], which may culminate in cellular death [159].

A recent study demonstrated that ablation of one copy of the BiP gene accelerates PrDs *in vivo* [160]. These effects correlated with a physical interaction between PrP and BiP, impacting prion replication. However, direct genetic manipulation of the UPR has provided unexpected results. Targeting XBP1 in the brain did not affect prion replication and its pathogenesis *in vivo* neither affected prion propagation, ER stress levels or neurodegeneration [161]. In contrast, Moreno and colleagues reported that persistent protein translational shutdown due to eIF2 $\alpha$  phosphorylation triggers synaptic dysfunction and neuronal death in scrapie prion-infected animals [162]. Gene therapy to deliver eIF2 $\alpha$  phosphatase provided neuroprotection in this model, whereas salubrinol treatment exacerbated the progression of the disease [162]. Furthermore, oral treatment with a specific inhibitor of PERK both at preclinical and symptomatic stages of Prion-infected mice attenuated disease progression [163]. Similarly, treatment of animals with

ISRIB, a small compound that blocks the consequences of eIF2 $\alpha$  phosphorylation protected against PrD [164]. Of note, PERK inhibition did not attenuate PrP misfolding, suggesting that its protection was specifically linked to synaptic function improvements. Overall data suggest that PrDs are associated with an ER stress response, where the PERK branch of the UPR may have a relevant contribution due to its role in controlling the synthesis of synaptic proteins.

## 8 Conclusion

The current state of the field indicates that understanding the relative impact of the UPR to PMDs is difficult to predict and requires systematic studies. Depending on the disease context and the signalling branch analysed, the UPR may have contrasting and even opposing effects. The identification of new drugs that directly interfere with UPR signalling in addition to the

possibility of brain *in vivo* manipulation of ER stress-associated genes in different animal models will provide information regarding the involvement of the UPR in PMD progression [165; 18]. Table 1 summarizes a collection of the most recent findings concerning UPR manipulation by pharmacological or genetic approaches and its outcome in disease progression of distinct PMDs animal models. Notably, UPR manipulation in various disease models has revealed unexpected and contrasting results depending on the disease context and the specific signalling molecule studied. Additionally, since the UPR has a major role in the physiology of many organs like pancreas, liver, and the immune system, serious side effects are predicted of the long-term administration of UPR-targeting drugs [2, 18]. Gene therapy is emerging as an interesting strategy to target the UPR locally in specific brain areas [166]. These tools will likely prove sufficient to clarify the causal relationship between ER proteostasis malfunction and the occurrence of PMDs. Importantly, available data suggests

**Table 1:** Functional studies linking ER stress with neurodegenerative diseases. A summary of selected most recent findings regarding the causality between UPR genetic or pharmacological manipulation and aggregation/toxicity of classical misfolded proteins in distinct NDDs.

Disease Model	UPR manipulation	Phenotype	Reference		
AD	Tg mice	Thapsigargin	Increased phosphorylation of tau, increased caspase-3 cleavage	57	
		JNK3 KO	Reduced amyloid $\beta$ , neuronal loss and cognitive dysfunction	42	
		PERK CNS KO	Improved learning and memory and LTP	52	
	APP/PS1 Tg mice	AAV-XBP-1	Rescued spine density, synaptic plasticity and memory function	50	
		Neuronal IRE1 $\alpha$ deletion	Improved learning and memory and LTP	43	
PD	$\alpha$ Syn Tg mice or AAV- $\alpha$ Syn infected rats	Salubrinal	Attenuates disease manifestation	70,73	
		Neurotoxins			
		ATF6 KO	Increased neurodegeneration	92	
		CHOP KO	Neuroprotection	7	
		AAV-BiP	Dopaminergic survival, decreased $\alpha$ Syn aggregation	93	
		AAV-XBP-1	Neuroprotection, reduced striatal denervation	86	
		PERK Het	Disease exacerbation, enhancement SOD1 aggregation	110	
ALS	SOD1 Tg mice	Salubrinal	Increased lifespan	103	
		ATF4 KO	Partial embryonic lethality, protection against disease progression	124	
		XBP1 CNS KO	Neuroprotection, extended life span, decreased SOD1 aggregation	102	
		Guanabenz	Accelerated disease progression	120	
		Guanabenz	Delayed disease onset, increased survival, less accumulation of aggregates, improved motor performance and attenuated motor neuron loss	121; 122	
			Sephin-1	Prevented the motor, morphological, and molecular defects	123
			ATF4 KO	No effect on aggregation	8
HD	Mutant Htt Tg mice	XBP1s CNS KO	Neuronal protection, improved motor performance, reduced Htt levels	8	
		AAV XBP1s	Decreased Htt aggregation	141	
PrDs	Scrapie Prion infection	Salubrinal	Disease exacerbation	162	
		XBP1s CNS KO	No effect on disease progression or prion replication	161	
		Caspase 12 KO	No effect on disease progression nor prion replication	153	
		AAV-GADD34	Global neuroprotection	162	
		PERK inhibitor	Reduces neurodegeneration and delays disease progression	163	
	ISRIB	Neuroprotection	164		

Abbreviations: AAV: adeno-associated virus; CNS: central nervous system; Het: heterozygous ; KO: knock out; LTP: long term potentiation; Tg: transgenic.

that ER stress may not only affect protein aggregation, but it may be also the direct cause of synaptic dysfunction as demonstrated in AD and PrDs. Since recent findings uncovered a novel role of XBP1 in enhancing learning and memory-related processes through the regulation of BDNF [51]. Thus, XBP1-based gene therapy may actually serve as a dual treatment to target proteostasis alteration, protein aggregation and synaptic function. eIF2 $\alpha$  phosphorylation and ATF4 have been also reported to influence cognitive process at the level of synaptic transmission and neuronal plasticity [167, 168]. The possible impact of the UPR in neuroinflammation and glial activation remains to be determined. In addition, interesting links between the UPR and energy control and global proteostasis control are also available that could be explored in the future in the context of neurodegenerative diseases.

**Acknowledgements:** This work was directly funded by FONDAP program 15150012, CONICYT-Brazil cooperation grant 441921/2016-7, Office of Naval Research-Global (ONR-G) N62909-16-1-2003, Millennium Institute P09-015-F, FONDEF D11I1007, and FONDEF ID16I10223. We also thank the support Muscular Dystrophy Association 382453, FONDECYT no. 1140549, and ALSRP Therapeutic Idea Award AL150111, U.S. Air Force Office of Scientific Research FA9550-16-1-0384, European Commission R&D, MSCA-RISE #734749. FCM is a postdoctoral fellow funded by FONDAP program 15150012.

**Conflict of Interest:** The authors state no conflict of interest.

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