

## Roles of Endoplasmic Reticulum Stress in Neurodegenerative Diseases

Soshi Kanemoto<sup>1\*</sup> and Hansen Wang<sup>2\*</sup>

<sup>1</sup>Department of Biochemistry, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8553, Japan  
<sup>2</sup>Faculty of Medicine, University of Toronto, 1 King's College Circle, Toronto, Ontario, Canada, M5S 1A8

### Abstract

The accumulation of misfolded proteins disrupts the functioning of endoplasmic reticulum (ER), leading to induction of the unfolded protein response (UPR) that protect cells against the toxic buildup of such proteins. However, prolonged stress due to the buildup of these toxic proteins induces specific cell death pathways. There is accumulating evidence implicating ER stress in the development and progression of neurodegenerative diseases. With the improved understanding of the underlying molecular mechanisms, therapeutic interventions that target the ER stress response would be potential strategies to treat neurodegenerative diseases.

### Introduction

The accumulation and aggregation of misfolded proteins is linked to occurrence of several neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and prion diseases [1-3]. The presence of misfolded proteins elicits cellular responses, including endoplasmic reticulum (ER) stress response that protects cells against the toxic buildup of misfolded proteins [3-6]. Accumulation of these proteins in excessive amounts, however, impairs the protective mechanisms designed to promote correct folding and degrade faulty proteins, ultimately leading to organelle dysfunction and cell death [3-6]. Emerging evidences have indicated that ER stress plays a pivotal role in the pathogenesis of neurodegenerative diseases.

### Endoplasmic Reticulum Stress Response

The ER is a specialized organelle that plays crucial roles in cell homeostasis and survival, including protein folding, lipid biosynthesis, and calcium and redox homeostasis [7-9]. The lumen of the ER is the major site for proper protein folding and contains molecular chaperones and folding enzymes including GRP78 (also known as Immunoglobulin binding protein, BiP), GRP94, protein disulfide isomerase (PDI), calnexin, and calreticulin. Only properly folded proteins are exported to the Golgi organelle, while incompletely folded proteins are retained in the ER to complete the folding process or are delivered to the cytosol to undergo endoplasmic reticulum associated degradation (ERAD). Under physiological conditions, there is equilibrium between ER protein load and folding capacity. Disturbances in ER homeostasis due to increased protein synthesis, accumulation of misfolded proteins, or alterations in the calcium or redox balance of the ER can cause a condition called ER stress [10-15].

In response to ER stress, cells have developed an adaptive signaling pathway called the unfolded protein response (UPR) or ER stress response [10,12,16]. Activation of the UPR causes a shutdown of global protein synthesis and activates mechanisms that allow the cells to deal with the accumulation of unfolded proteins. The protein folding capacity is enhanced by increasing the expression of ER chaperones, and the degradation of misfolded proteins is also upregulated. The coordinated biochemical response to ER stress allows cells to cope with ER stress. However, if the stress is prolonged or excessive, the UPR initiates apoptosis [8,10,12,16]. There are three major branches of UPR, which are each activated by a dedicated ER localized transmembrane molecule: IRE1 (Inositol Requiring Enzyme-1), PERK (Protein Kinase RNA- like ER Kinase) and ATF6 (Activating Transcription Factor 6) [8,17]. IRE1 and PERK are type I transmembrane proteins with protein kinase activity, whereas ATF6 is a type II transmembrane protein encoding a transcription factor [12]. Activation of IRE1, PERK and

ATF6 initiates a network of intracellular signalling pathways during the UPR [13,14].

IRE1 is the conserved ER stress sensor from yeast to mammalian. Under physiologic conditions, it is in inactive form through an interaction with GRP78/BiP [12-14]. Upon accumulation of unfolded proteins in the ER lumen, GRP78/BiP dissociates from IRE1, leading to its activation by trans-autophosphorylation [17]. IRE1 has a cytoplasmic endoribonuclease domain, which, upon activation, splices and enables the translation of the mRNA encoding X-box binding protein-1 (XBP1). Spliced XBP1 is a transcription factor that induces many essential UPR genes that increase ER folding capacity and expand ER membrane surface area [7,8,13,14]. Recently IRE1 has been shown to be required for cleavage and post-transcriptional degradation of mRNAs, which may function as another mechanism to reduce protein load on the ER [18]. The other functions of IRE1 are related to the triggering of apoptosis. Upon activation, IRE1 binds the adaptor protein, TNF receptor-associated factor 2 (TRAF2), which then promotes activation of c-Jun N-terminal kinase (JNK) through apoptosis signal-regulating kinase-1 (ASK1) [19]. Additionally, IRE1 activation has been shown to trigger the recruitment of a proapoptotic ER-resident cysteine protease, caspase 12 [20].

PERK is a serine threonine kinase and similar to IRE1. It has a luminal ER stress-sensing domain and is activated through trans-autophosphorylation. Activated PERK phosphorylates eukaryotic translation initiation factor 2 $\alpha$  (eIF2 $\alpha$ ), which results in global translational attenuation and reduced ER protein load [12-14]. However, phosphorylated eIF2 $\alpha$  promotes the translation of ATF4, which induces the UPR effector CHOP (C/EBP $\alpha$ -homologous protein, also known as GADD153). In pathological settings, prolonged CHOP expression triggers apoptosis through a number of mechanisms, including down-regulation of the anti apoptotic factor B cell

**\*Corresponding authors:** Dr. Hansen Wang, Faculty of Medicine, University of Toronto, 1 King's College Circle, Toronto, ON M5S 1A8 Canada, E-mail: [hansen.wang@utoronto.ca](mailto:hansen.wang@utoronto.ca)

Dr. Soshi Kanemoto, Department of Biochemistry, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8553, Japan, E-mail: [soshikanemoto@hiroshima-u.ac.jp](mailto:soshikanemoto@hiroshima-u.ac.jp)

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lymphoma-2 (Bcl-2) and induction of a calcium-mediated apoptosis pathway triggered by the CHOP transcriptional target, ER oxidase-1 $\alpha$  [11,13,14].

ATF6, once activated under ER stress condition, translocates to the Golgi complex, where it gets cleaved by site 1 and site 2 proteases. The resultant N-terminal fragment of ATF6 migrates to the nucleus, and function as transcription factor, which activates transcription of XBP1 and molecular chaperones such as GRP78/BiP and GRP94 [9,12-14].

## Endoplasmic Reticulum Stress and Pathogenesis of Neurodegenerative Disorders

The ER has essential roles in physiologic regulation of many processes. Accumulating evidence indicates that pathological conditions that interfere with ER homeostasis give rise to chronic activation of ER stress response/UPR, which contributes to the pathogenesis of neurodegenerative disorders [3,4,6,21,22].

### Alzheimer's disease

AD is a progressive neurologic disorder characterized by a decline in cognitive processes, eventually leading to dementia. The hallmarks of this disease are accumulation of extracellular amyloid- $\beta$  peptides and intracellular aggregates of phosphorylated tau proteins, along with the perturbation of calcium homeostasis and neuronal death [23,24]. Genetic studies have revealed that there are three causative genes associated with the familial forms of the disease, which are amyloid- $\beta$  precursor protein (APP), presenilin1 (PS1) and presenilin2 (PS2). Mutations in these proteins lead to alterations in the processing of amyloid- $\beta$  peptides from APP, resulting in more toxic forms of amyloid- $\beta$  peptides in the plaques. Intranuclear accumulation of amyloid- $\beta$ , an early pathological change in Alzheimer's disease, has been shown to cause cell death by inducing ER stress, endosomal/lysosomal leakage, and mitochondrial dysfunction [25]. Mutations in the PS1 gene interfere with the physiologic functions of ER stress response and render cells more susceptible to ER stress induced death [26]. In mice with mutant PS1, ER stress response is enhanced and level of CHOP is elevated, and contributes to the pathogenic actions of PS1 mutations [27]. ER stress response is activated in the brain of AD patients [28,29]. The UPR activation markers are observed in neurons with diffuse staining of phosphorylated tau protein. The ER stress response in AD neurons occurs at an early stage of neurofibrillary degeneration, suggesting that the prolonged activation of ER stress response is involved in both tau phosphorylation and neurodegeneration in AD pathogenesis [28,29]. One recent study further suggested that ER stress and hyperphosphorylation of tau could be induced by each other, thus a vicious cycle is formed to propagate neurodegeneration associated with AD [30]. However, the exact role of ER stress response in the pathogenesis of AD must await further studies in suitable animal models.

### Parkinson's disease

PD is a neurodegenerative disorder characterized by the death of dopaminergic neurons and accumulation of protein aggregates (Lewy bodies, LBs) in a distinct brain region. Currently, studies have shown that dysfunction of ER stress response have essential roles in the pathogenesis of this disease [28,31,32]. Missense mutations in the gene coding for  $\alpha$ -synuclein cause dominant familial PD. The A53T mutation is associated with ER stress response as evidenced by increased expression of CHOP and GRP78/BiP and increased phosphorylation of eIF2 $\alpha$ , suggesting ER stress response is active in these cells [33]. Inhibition of phosphorylation of eIF2 $\alpha$  protected the A53T  $\alpha$ -synuclein

over expressing cells from cell death, suggesting that ER stress response was shifting the balance towards apoptosis [33]. Recent studies further indicate that the accumulation of  $\alpha$ -synuclein within ER leads to chronic ER stress conditions that contribute to neurodegeneration in PD and other alpha-synucleinopathies [34,35]. Similarly, evidences have indicated that protein products of genes mutated in PD, such as ubiquitin carboxyl-terminal esterase L1 (UCHL1), leucine-rich repeat kinase 2 (LRRK2), Parkinson protein 2 (Parkin), PTEN-induced kinase 1 (PINK1) and DJ-1, play a role in regulating protein stability and ER stress response [22,31,32]. Additionally, drugs such as 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>) which are used to develop animal models of PD, induce ER stress [36-38]. Therefore, ER stress response is a key cellular function that is disrupted and this dysfunction leads to neuronal cell death in familial and sporadic PD.

### Amyotrophic lateral sclerosis

ALS is characterized by muscle weakness, atrophy, and paralysis. The pathologic feature of ALS is the selective degeneration of motor neurons in brain and spinal cord [39,40]. Mutations in the superoxide dismutase-1 (SOD1) gene have been linked to the familial form of ALS. In transgenic mice of mutated SOD1 (mSOD1), misfolding and aggregates of mutated SOD1 induces ER stress response and causes apoptosis [39,41] and has been implicated in the development of ALS. PDI (also functions as an ER chaperon) was increased and co-localized with aggregated mSOD1 protein [42]. Activation of ATF6 $\alpha$  and XBP1 and phosphorylation of eIF2 $\alpha$  were also detectable in mSOD1(G93A) motor neurons [43]. Furthermore, motor neurons were shown to be selectively prone to ER stress response and axonal degeneration [40]. Dysfunction of ERAD, causing ER stress has been shown to occur in mSOD1 containing motor neurons through Derlin-1. The mSOD1 was shown to interact with Derlin-1, causing dysregulation of ERAD which leads to ER stress induced ASK1 activation, apoptosis and disease progression [44]. Mutation of the vesicle-associated membrane protein B (VAPB), an ER transmembrane protein involved in ER stress regulation, cause some cases of familial ALS [45]. Expression of wild-type and ALS linked mutant VAPB selectively triggers death of motor neurons through a Ca<sup>2+</sup> dependent ER associated pathway [46]. Development of ALS may occur due to the disruption of the ER stress response caused by the mutation in VAPB, resulting in accumulation of misfolded protein in the ER [47]. Native VAPB has been implicated in the UPR via the IRE1/XBP1 [47], and ATF6 pathways [48], a function that is lost for misfolded mutant VAPB (P56S) [47,48]. It was found that both VAPB and mutant VAPB (P56S) directly interact with ATF6 and reduce the ability of ATF6 to promote transcription of XBP1, with the mutant as a more potent ATF6 inhibitor [48]. The induction of ER stress response has been observed in human sporadic ALS [49]. The ER stress sensors IRE1, PERK and ATF6 show increased expression in spinal cord from sporadic ALS patients [49]. However, further studies are needed to elucidate the exact mechanisms responsible for ER stress response and its pathological consequences in ALS.

### Huntington's disease

HD is an autosomal dominant neurodegenerative disease characterized by motor abnormalities, and onset of psychiatric symptoms and dementia in early- to mid-adult life. It represents one of polyglutamine (polyQ) repeat diseases that cause region-specific neuronal degeneration [50,51]. The glutamine expansion of approximately more than 40 repeats within the Huntingtin (Htt) protein confers a dominant gain of toxic function, leading to progressive accumulation of misfolded mutant Htt (mHtt) in the

form of intracellular oligomers and inclusions, and to neuronal loss [1,52,53]. Although the mechanisms through which misfolded mHtt cause neuronal toxicity are still controversial, recent studies in cellular and animal models of HD suggest a direct correlation between disease progression and ER stress [5,53]. It has been demonstrated that inhibition of wild-type Htt expression drastically alters the structure of the ER network and trafficking, suggesting that its biological function is related to this organelle [54]. The expression of mHtt or expanded polyQ peptides leads to ER stress mediated apoptosis in cellular models of HD [55-58]. The expression of ER stress related markers, including GRP78/BiP, CHOP and HERP, is increased at the mRNA level in postmortem brains of HD patients [59]. The increase of ER stress was also observed in HD mouse models even at the early stage of the disease [59,60]. In addition, altered ER calcium homeostasis was found in HD mouse models [61]. Notably, processing of ATF6 $\alpha$  is impaired in both animal models and in post-mortem tissue from HD patients, which may reduce the ability of neurons to adapt to ER stress [62]. Activation of the PERK/eIF2 $\alpha$  UPR branch triggers the degradation of polyQ peptides by autophagy, a process for degradation of HD-linked protein aggregates [56]. However, the autophagy activity is impaired in mHtt expressing neurons partially due to a failure of autophagosomes to recognize their cargos, which may result in general alterations in protein homeostasis [63]. Although the progression of HD correlates with the occurrence of ER stress response, the actual characterization of ER stress in HD is still incomplete.

### Prion diseases

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of fatal and infectious neurodegenerative diseases. The central event in prion diseases is the misfolding, aggregation, and brain accumulation of the prion protein [64, 65]. Prion protein (PrP) exists in at least two conformational states, the normal cellular form (PrP<sup>c</sup>) and an abnormal infective form (PrP<sup>Sc</sup>). The abnormal PrP<sup>Sc</sup> differs from the normal cellular form only in its three-dimensional conformation, having a higher  $\beta$ -sheet structure than the native protein [64-66]. Both PrP<sup>c</sup> and PrP<sup>Sc</sup> are involved in neurodegeneration associated with prion diseases [67-71]. The expression of ER stress markers, such as GRP78/BiP, GRP94 and GRP58, is upregulated in the cerebral cortex of prion disease patients, suggesting that ER stress response may participate in the pathogenesis of prion diseases [70]. PrP<sup>Sc</sup> purified from brains of scrapie-infected mice can induce ER stress response and apoptosis. Alteration of ER Ca<sup>2+</sup> homeostasis and subsequent ER stress has also been implicated in the progression of prion diseases [69,70]. PrP<sup>Sc</sup> induces the release of cytosolic Ca<sup>2+</sup> mainly from the ER, which leads to loss of mitochondrial membrane potential, increased ROS and cell death. This release of Ca<sup>2+</sup> is dependent on the apoptosis triggering domain (residues 106-126) of prion protein [67-69]. Autophagy plays an important role in targeting cellular proteins, protein aggregates and organelles for degradation for cell survival. Reticulon 3 (RTN3), an ER-localized protein, which is activated under ER stress in prion diseases, attenuates the clearance of cytosolic prion aggregates via inhibiting autophagy and thus may further enhance ER stress [72]. These studies suggest that ER stress is involved in neurodegeneration associated with prion disease.

### Therapeutic Implications

The ER function is perturbed in many pathological processes. Alleviating ER stress through enhancement of ER function may protect cells from damage and ameliorate disease. Valproate, a drug used in epilepsy treatment, increases the expression of ER chaperones, such as GRP78/BiP and GRP94, and has shown beneficial effects in

models of neurodegenerative diseases [73]. Consistent with the model in which components of the ER stress response favor neurotoxicity, targeting individual molecules in UPR Pathways could be an option for treatment of neurodegenerative diseases. Glycogen synthase kinase-3 (GSK3) plays a central role in signaling downstream effects of ER stress. It was found that valproate can protect cells from ER stress-induced apoptosis by inhibiting GSK3 [74]. Salubrinal, a small molecule which inhibits dephosphorylation of eIF2 $\alpha$  and protects cells from ER stress [75], also attenuates the neurodegeneration in mouse model of familial ALS [40]. The XBP1 deficiency in the nervous system has been shown to be protective in a mouse model of ALS due to an enhanced clearance of mutant SOD1 aggregates by autophagy [76]. The protective effects of XBP1 deficiency have also been seen in both cellular and animal models of HD. The protective effects are associated with enhanced autophagy [77]. ASK1 is a key element in ER stress-induced cell death that plays an important role in the neuropathological alterations in polyQ diseases [57]. Inhibition of ASK1 reduces ER stress and nuclear Htt fragments in a mouse model of HD [60]. Down-regulation of RTN3 promotes the clearance of cytoplasmic PrP aggregates and alleviates ER stress, the apoptosis due to the cytoplasmic PrP aggregates is inhibited accordingly, suggesting that RTN3 negatively regulates autophagy to block the clearance of cytoplasmic PrP aggregates and may serve as a target for inducing autophagy to treat prion diseases [72]. These studies thus provide evidence for therapeutic potentials of targeting ER stress response in neurodegenerative disorders.

### Conclusions

There are compelling evidences suggesting that signal pathways of ER stress response are important in the pathogenesis of neurodegenerative diseases. However, many unanswered questions remain [5,8,78]. Understanding the pathways by which misfolded proteins cause neurodegeneration is essential for developing efficient treatments for neurodegenerative disorders. On the other hand, although targeting ER stress may be beneficial for patients with neurodegenerative disorders, new therapeutic agents must be carefully screened and tested in appropriate disease models to avoid possible adverse effects [5,21,22,34].

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