

Review Article

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Link between endoplasmic reticulum stress and autophagy in neurodegenerative diseases

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Abstract: Increasing evidence suggests that endoplasmic reticulum (ER) stress and autophagy play an important role in regulating brain function. ER stress activates three major branches of the unfolded protein response (UPR) pathways, namely inositol-requiring enzyme-1 (IRE1), double stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK) and activating transcription factor 6 (ATF6)-mediated pathways. Recent studies have suggested that these UPR signals may be linked to autophagy. In this review article, we summarize recent evidence and discuss a possible link between ER stress and autophagy with regard to neurodegenerative diseases. Furthermore, possible pharmacological strategies targeting UPR and autophagy are discussed.

Keywords: Endoplasmic reticulum stress, Unfolded protein response, Neurodegenerative diseases, Autophagy

Abbreviations

a disintegrin and metalloproteinase 10 (ADAM10), Alzheimer's disease (AD), amyloid precursor protein (APP), Amyotrophic lateral sclerosis (ALS), apoptosis-signal-regulating kinase (ASK1), activating transcription factor 4 (ATF4), activating transcription factor 6 (ATF6), Atg14-like protein (Atg14L), autophagy-related 12 (Atg12), autophagy-related 3 (Atg3), autophagy-related 5 (Atg5), autophagy-

related 7 (Atg7), β -site amyloid precursor protein cleaving enzyme 1 (BACE1), B-cell CLL/lymphoma 2 (BCL2), BCL2 homology domain 3 (BH3), Beclin 1 (BECN1), brain-derived neurotrophic factor (BDNF), C/EBP-homologous protein (CHOP), Central Nervous System (CNS), death-associated protein kinase 1 (DAPK1), eukaryotic initiation factor 2 (eIF2 α), ER-associated degradation (ERAD), endoplasmic reticulum (ER), Huntington's disease (HD), 3-hydroxy-3-methylglutaryl-coenzyme A reductase degradation 1 (HRD1), Interferon-gamma (IFN- γ), inositol-requiring enzyme-1 (IRE1), c-Jun N terminal kinase (JNK), Kelch-like ECH-associated protein 1 (Keap1), light chain 3 (LC3), microtubule-associated protein 1 light chain 3 (MAP1LC3B), mitogen-activated protein kinase kinase kinase (MAPKKK), mitogen-activated protein kinases (MAPKs), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), neurodegenerative disease (ND), nuclear factor erythroid 2-related factor 2 (Nrf2), 6-hydroxydopamine (6-OHDA), Parkinson's disease (PD), double stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK), progressive supranuclear palsy (PSP), regulated intramembrane proteolysis (RIP), Reactive Oxygen Species (ROS), site 1 protease (S1P), site 2 protease (S2P), spliced XBP1 (sXBP1), substantia nigra pars compacta (SNpc), TNF-receptor-associated factor 2 (TRAF2), unfolded protein response (UPR), X-box binding protein 1 (XBP1)

1 Introduction

With the increasing senescent population, the incidence of neurodegenerative diseases has increased worldwide. Among neurodegenerative disease such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), the treatment of AD seems to be particularly challenging, since the number of patients is larger and the currently available medicines have limited therapeutic effects. Following elucidation of the pathological mechanism of AD, novel therapeutics could be developed. The endoplasmic reticulum (ER) is an organelle involved in protein folding as well as regulation of Ca²⁺ homeostasis.

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When cells are exposed to stressful stimuli that perturb the protein-folding capacity in the ER, it leads to the accumulation of unfolded proteins causing ER stress (1). Triggered by the ER stress, the unfolded protein response (UPR) is activated in the cell. There is increasing evidence for the involvement of ER stress in various diseases such as neurodegenerative diseases, diabetes, obesity, and cancer (2-5). In the context of neurodegenerative diseases, the present review describes the recent findings of the mechanisms of UPR, ER stress as a causative for neurodegenerative diseases, ER stress-induced apoptosis and autophagy involved in ER stress. This review also describes the pharmacological strategy for treating AD.

2 ER stress-induced unfolded protein response

In a stress-exposed cell, the three major components of UPR, namely, inositol-requiring enzyme-1 (IRE1), double stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK) and activating transcription factor 6 (ATF6) are ER stress sensor proteins. These proteins are present in the ER and are activated in response to

unfolded protein accumulation in the ER. Activation of IRE1 induces X-box binding protein 1 (XBP1) mRNA splicing in the cytosol and the spliced XBP1 (sXBP1) acts as a transcription factor (6). PERK activation leads to eukaryotic initiation factor 2 (eIF2 α) phosphorylation and attenuates translation, thereby reducing the accumulation of unfolded proteins (7, 8). As a response to ER stress, regulated intramembrane proteolysis (RIP) activates ATF6 (9-11). Once activated, ATF6 translocates to the Golgi to be digested by two proteases, namely, site 1 protease (S1P) and site 2 protease (S2P) (9-11). The cleaved fragment (p50ATF6) functions as a transcription factor and induces UPR-related genes (12). Additionally, the ER-associated degradation (ERAD) pathway is activated to degrade the unfolded proteins through the ubiquitin-proteasome system (13-15).

3 ER stress and apoptosis

Several mechanisms have been reported regarding the roles of the three major ER stress sensor proteins in the ER stress-induced apoptotic response. These have been summarized as follows (Fig. 1).

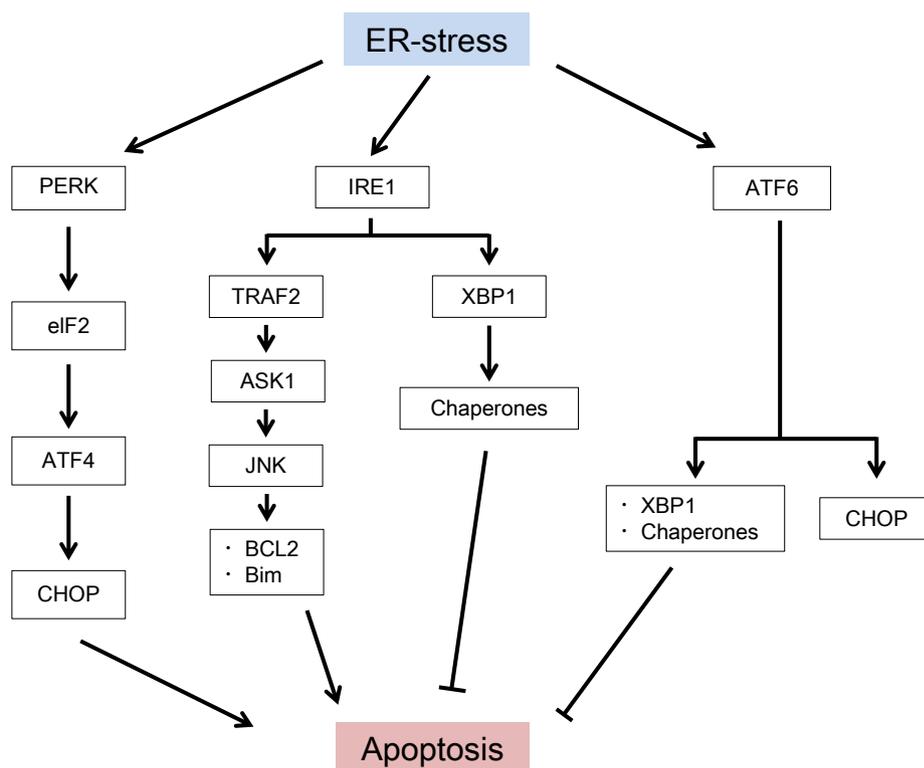


Figure 1. The link between the three major branches of UPR (PERK, IRE1, and ATF6), and apoptosis. PERK branch of UPR induces CHOP production and apoptosis. IRE1 branch of UPR induces JNK activation, which in turn induces apoptosis. IRE1 branch of UPR also induces XBP1 splicing, which is involved in inhibiting apoptosis. ATF6 branch of UPR induces production of XBP1 and chaperone transcripts and may be involved in attenuating apoptosis.

3.1 PERK

In addition to inhibition of translation, PERK also leads to induction of ATF4 translation, thereby promoting cell survival by inducing several genes involved in amino-acid metabolism, redox reactions, stress response and protein secretion (16). On the other hand, ATF4 also induces C/EBP homologous protein (CHOP) and promotes apoptotic cell death (17). Therefore, activation of PERK may play a key role in cell survival and also in switching pro-survival to pro-apoptotic signaling by induction of CHOP during ER stress.

3.2 IRE1

The activated IRE1 induces sXBP1 activation, which has diverse targets such as ER chaperones and the HSP40 family member P58IPK (18). IRE1 not only leads to cell survival but also induces apoptotic cell death (19). IRE1-induced cell death is caused by activation of the c-Jun N-terminal kinase (JNK) pathway (20). Active IRE1 forms the IRE1-TNF receptor-associated factor 2 (TRAF2) complex during ER stress, which induces the apoptosis-signal-regulating kinase (ASK1). ASK1 is a mitogen-activated protein kinase kinase (MAPKKK) that has been shown to relay various stress signals downstream of mitogen-activated protein kinases (MAPKs) such as JNK and p38 (21). Activation of JNK under ER stress is known to induce cell death through the regulation of B-cell CLL/lymphoma 2 (BCL2) family of proteins (22). For example, JNK leads to phosphorylation of BCL2 and suppresses its anti-apoptotic activity (23). In addition to BCL2, JNK also phosphorylates BCL2 homology domain 3 (BH3)-only members of the BCL2 family, such as Bim, leading to apoptosis (24).

3.3 ATF6

So far, the identified targets of ATF6 include the transcription factors CHOP and XBP1 (12). Although ATF6 plays a key regulatory step in transcriptional induction of CHOP and XBP1, as well as ER chaperones, its cytotoxic effects have not been clearly described.

4 ER stress and autophagy

Cells respond to ER stress through the activation of UPR. However, severe ER stress is regulated by the activation of apoptotic signals to lower stress load (1). Nevertheless, the underlying regulatory mechanisms the cells face

during ER stress are still an enigma. Interestingly, there is evidence that links ER stress and autophagy. Autophagy degrades cytoplasmic components, proteins and organelles by fusing them with lysosomes (25). The activation of autophagy could result in the degradation of unfolded proteins and assisting cells to cope with stress load. Consistent with this hypothesis, defective autophagy due to autophagy-related 7 (Atg7) deficiency was shown to cause ER stress in the liver (26). Autophagy has been implicated as a key factor in neurodegenerative diseases. Autophagy-related 5 (Atg5) or 7 (Atg7) deficiencies in the central nervous system has been shown to cause neurodegenerative disease in mice (27, 28). On the other hand, induction of autophagy through inhibition of mTOR was shown to confer protection against toxicity of polyglutamine expansions in the HD models (29). Moreover, induction of autophagy was also shown to increase neuronal survival in an ALS model (30). p62 (Sqstm1) is involved in selective autophagy (31, 32) and has been reported to be involved in neurodegenerative diseases. Its deficiency causes age-dependent accumulation of phosphorylated Tau and it may, thus, be involved in neurodegeneration (33). Regarding the precise role of autophagy in neurodegenerative diseases, several excellent reviews have been published (34, 35). Altogether, these observations suggest that autophagy may be involved in neurodegenerative diseases. Additionally, ER stress was also shown to induce autophagy in a manner dependent on the IRE1 and JNK-dependent pathway, and the inhibition of autophagy resulted in increased vulnerability of cells to ER stress-induced death (36). Recent studies have demonstrated a mechanistic link between ER stress and autophagy. In various diseases, the activation of PERK plays an important role in inducing autophagy to degrade the unfolded proteins. PERK-mediated activation of ATF4 leads to upregulation of some of the autophagy genes, including microtubule-associated protein 1 light chain 3 (MAP1LC3B), Beclin 1 (BECN1), autophagy-related 3 (ATG3) and autophagy-related 12 (ATG12). Another component of UPR signaling, IRE1, also induces autophagy by the activation of MAPK8 which disrupts the interaction of BECN1 and BCL2 via phosphorylation of BCL2 (37). In addition, activated ATF6, under ER stress, increases the expression of death-associated protein kinase 1 (DAPK1), which phosphorylates BECN1. Phosphorylation of BECN1 results in reduction of its affinity for BCL2 and triggers autophagy (Fig. 2). Therefore, one of the mechanisms regulating cell fate during ER stress may be mediated through the autophagic pathway. In the present review, we summarize and discuss ER stress and autophagy with a special focus on neurodegenerative diseases.

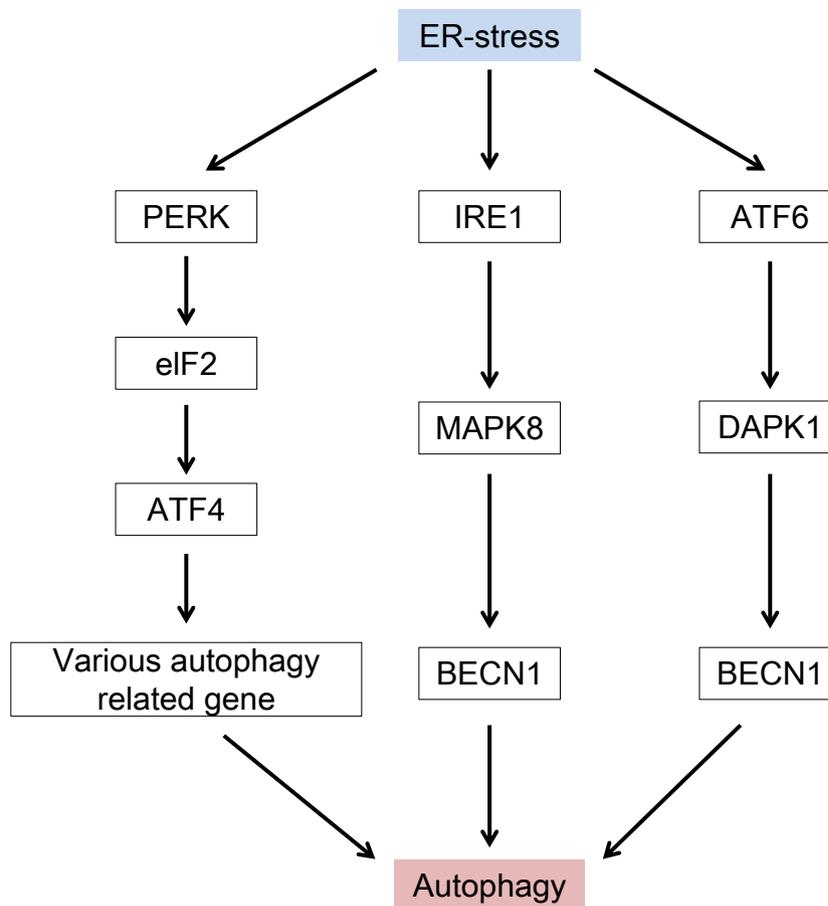


Figure 2. The possible link between the three major branches of UPR (PERK, IRE1, and ATF6) and autophagic response. Several reports indicate that ER stress sensor proteins such as PERK, IRE1, and ATF6 are involved in regulating autophagy.

5 Autophagy and ER stress in neurodegenerative diseases

Several reports indicating a possible link between ER stress and autophagy in neurodegenerative diseases are associated with AD, PD and HD. Among the three different UPR pathways (IRE1, PERK, and ATF6), the IRE1-sXBP1 arm is the most well-studied in the context of autophagy and neurodegenerative diseases. An important link, in the PERK signaling, between Keap1 and Nrf2 was suggested. In the following section, we will mostly focus on these UPR pathways and discuss autophagy and ER stress in the context of neurodegenerative diseases.

5.1 XBP1 and neurodegenerative diseases

BECN1, which was originally identified as a Bcl-2-interacting protein (38), also interacts with several autophagy-related proteins such as Atg14-like protein

(Atg14L) and Rubicon (39), thus inducing autophagy (40). The UPR protein sXBP1 was shown to bind directly to the promoter region of BECN1 and upregulate its transcription (41). Therefore, the IRE1-sXBP1 arm of the UPR may regulate the induction of BECN1 and may thereby activate the autophagic response. Importantly, a decrease in the expression levels of BECN1 was observed in AD patients as well as mouse models of AD. The overexpression of BECN1 in mice showed a reduced AD pathology (42). Furthermore, the heterozygous deletion of BECN1 in an amyloid precursor protein (APP) transgenic AD mouse model resulted in exacerbation of neurodegeneration (42). Similarly, in the α -synuclein mouse model of PD, BECN1 overexpression ameliorated the pathology (43). Moreover, a BECN1 knockdown increased the accumulation of mutant Huntingtin in the HD mouse model (44). These observations suggest that BECN1 in the Central Nervous System (CNS) may be involved in the pathogenesis of neurodegenerative diseases. XBP1 was reported to protect against AD pathology; it was shown that transduction

of hippocampus with sXBP1 rescued alterations in spine density, synaptic plasticity and memory loss in an AD mouse model (45). Several mechanisms for the amelioration of AD pathology by sXBP1 have been proposed; one such mechanism is the induction of disintegrin and metalloproteinase 10 (ADAM10) by sXBP1 (46). Furthermore, sXBP1 was shown to reduce the level of β -site amyloid precursor protein cleaving enzyme 1 (BACE1), which plays a key role in A β production (47). The reduction of BACE1 level is mediated through the ubiquitin-ligase 3-hydroxy-3-methylglutaryl-coenzyme A reductase degradation 1 (HRD1) (47) which is also involved in APP degradation and the subsequent reduction in A β production (48). Moreover, sXBP1 enhances memory formation possibly by increasing the production of brain-derived neurotrophic factor (BDNF) in the CNS (49). In addition to these mechanisms, sXBP1-induced BECN1 activation and subsequent activation of autophagy may be one of the mechanisms for ameliorating AD pathology (Fig. 3). Also, there have been reports that sXBP1 can confer protection against dopaminergic neuronal death in PD and that adenoviral sXBP1 overexpression attenuates dopaminergic neuronal death in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse models of PD (50). Furthermore, sXBP1 delivered to substantia nigra pars compacta (SNpc) through adeno-associated viral vectors conferred protection against 6-hydroxydopamine (6-OHDA)-induced dopaminergic neuronal death (51).

5.2 PERK and neurodegenerative disease

In addition to XBP1, PERK-eIF2 α signaling is involved in the induction of autophagy in an HD mouse model. It has been reported that polyQ72-induced light chain 3 (LC3) conversion is attenuated by dominant negative PERK (52). Furthermore, Atg12 mRNA was reported to be induced by polyQ72 (52). The ATF6 arm of UPR was shown to be involved in interferon-gamma (IFN- γ)-induced activation of DAPK1 and autophagy (53). However, the underlying regulatory mechanisms of ATF6-mediated activation of autophagy, and their role in neurodegenerative diseases, are currently not well-understood.

5.3 Keap1-Nrf2 pathway

The Kelch-like ECH-associated protein 1 (Keap1)-nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is activated under oxidative stress and plays a role in protecting the cells against oxidative damage (54, 55). Under stressful conditions, Keap1 and Nrf2 dissociate, and Nrf2 translocates to the nucleus, inducing antioxidant genes (56). A link between p62-mediated autophagy and the Keap1-Nrf2 pathway has been reported. Phosphorylation of the Ser351 residue of p62 increases its binding to Keap1, thereby enhancing the dissociation of the Keap1-Nrf2 complex which subsequently induces the Nrf2 target gene (57). Furthermore, p62 protects

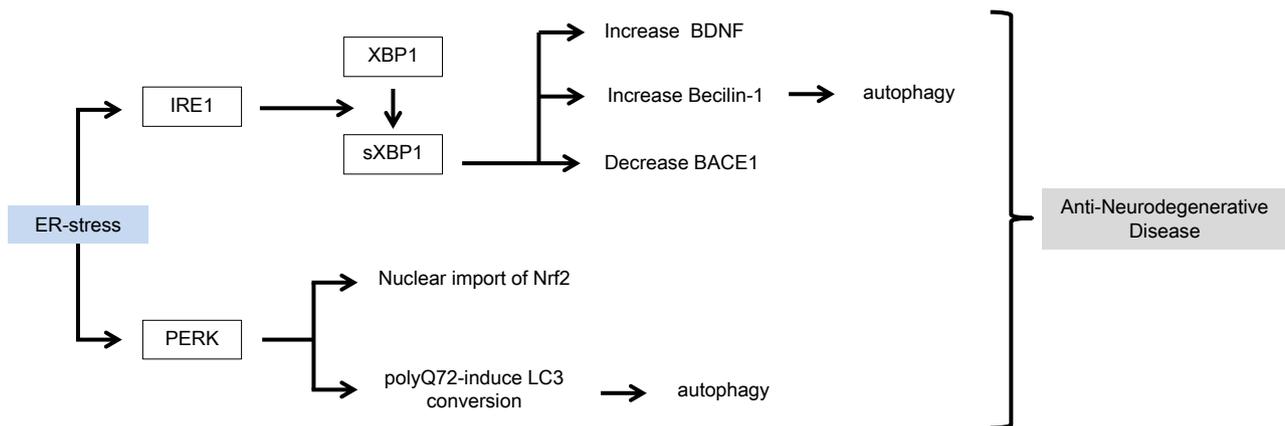


Figure 3. Possible mechanisms through which the IRE1-XBP1 and PERK-eIF2 α arms of UPR may influence pathogenesis of neurodegenerative diseases. Activation of IRE1 induces XBP1 splicing. The spliced form of XBP1 (sXBP1) functions as a transcription factor and activates BECN1 which induces autophagy. Induction of autophagy ameliorates neurodegenerative diseases. In addition, sXBP1 increases BDNF and may ameliorate neurodegenerative diseases. Furthermore, sXBP1 may decrease BACE1 levels through HRD1, thereby reducing amyloid β production and ameliorating Alzheimer's disease. Activation of PERK enhances the nuclear import of Nrf2 which plays a role in protecting the cells against oxidative damage. Activation of PERK mediates polyQ72-induced LC3 conversion which is involved in the induction of autophagy.

against ER stress-induced cell death by regulating the Keap1-Nrf2 pathway (58). In a neurodegenerative model, p62 was shown to ameliorate AD-like pathology through regulation of p62-mediated selective autophagy in mice (59). Interestingly, Nrf2 complex is a direct target of PERK that, when activated, dissociates the Keap1-Nrf2 complex and enhances the nuclear import of Nrf2 (60). This PERK-Nrf2 pathway may play a role in cell survival against ER stress (60, 61). Furthermore, PERK was shown to be involved in the tauopathy progressive supranuclear palsy (PSP) (62, 63) and PERK activator-induced Nrf2 signaling was suggested to ameliorate PSP (64). In addition to PERK, sulfenylation of IRE1 by reactive oxygen species (ROS) was suggested to activate Nrf2 (SKN-1 in *C. elegans*) and induce an antioxidant response (65). Overall, UPR, Keap1-Nrf2 signaling and p62-mediated autophagy may play important roles in neurodegenerative diseases (Fig. 3).

Knowledge of the mechanisms underlying these signals is still in its infancy. The precise mechanisms, and the possible connection between UPR and the autophagic pathway in the context of pathogenesis of neurodegenerative diseases may require further elucidation in future studies.

6 A possible pharmacological strategy for treating neurodegenerative diseases

As noted above, autophagy and ER stress pathway may be involved in the pathogenesis of neurodegenerative diseases. Therefore, one of the possible strategies for treating neurodegenerative diseases may be to upregulate the autophagic pathway. Furthermore, activating several UPR components, such as sXBP1, may also be beneficial. However, developmental ablation of XBP1 in the CNS was shown to cause resistance to 6-OHDA-induced neuronal death (51). Interestingly, the developmental ablation of XBP1 caused a compensatory upregulation of several other UPR components; this compensatory upregulation may cause a proteostatic alteration in order to resist stress (66). These results suggest that inhibition of the IRE1-sXBP1 pathway before the onset of disease may also be beneficial for treatment. Currently, it is unclear as to which of the approaches, inhibition or activation of IRE1-XBP1 pathway, is beneficial for ameliorating neurodegenerative diseases and further understanding of the role of sXBP1 in neurodegenerative diseases may be required.

The association between a cell-permeable autophagy-inducing peptide, Tat-BECN1, and autophagic signaling has been reported. This peptide was found to reduce the accumulation of polyglutamine expansion protein aggregates by activating autophagy (67). Therefore, in addition to sXBP1-induced BECN1 expression (41), Tat-BECN1 would also be an attractive target for therapeutic intervention.

7 Concluding remarks

Stress exposure causes accumulation of unfolded proteins and this accumulation is one of the key mechanisms underlying the cause of neurodegenerative diseases. In the present review, we discussed how cells respond to stress by focusing on the crosstalk between ER stress and autophagy. Targeting ER stress/autophagy would be an attractive therapeutic approach for neurodegenerative diseases as it may be able to reduce the accumulation of unfolded proteins in the cells. As also discussed, current research on ER stress/autophagy is still in its infancy. Further studies are warranted to elucidate the crosstalk between ER stress and autophagy and novel strategies that can regulate this crosstalk could be utilized in treating neurodegenerative diseases. Based on these concepts, we believe that a novel compound for the treatment of neurodegenerative diseases can be developed.

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