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REVIEW

The unfolded protein response in Alzheimer's disease

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Abstract Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic dysfunction and accumulation of amyloid-beta (Aβ) peptide, which are responsible for the progressive loss of memory. The mechanisms involved in neuron dysfunction in AD remain poorly understood. Recent evidence implicates the participation of adaptive responses to stress within the endoplasmic reticulum (ER) in the disease process, via a pathway known as the unfolded protein response (UPR). Here, we review the findings suggesting a functional role of ER stress in the etiology of AD. Possible therapeutic strategies to mitigate ER stress in the context of AD are discussed.

Keywords Alzheimer's disease · Amyloid-β · APP · Protein misfolding · ER stress · UPR

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Abbreviations

Aβ	Amyloid beta
AD	Alzheimer's disease
AICD	APP intracellular domain
ALS	Amyotrophic lateral sclerosis
APH1	Anterior pharynx defective 1
APP	Amyloid precursor protein
ATF4	Activating transcription factor 4
ATF6	Activating transcription factor 6
BACE1	β-site APP cleaving enzyme-1
BiP/Grp78	Glucose-related protein at 78 kDa
Cdk5	Cyclin-dependent kinase 5
CHOP/GADD134	C/EBP-homologous protein
eIF2α	Eukaryotic translation initiator factor 2α
ER	Endoplasmic reticulum
ERAD	ER-associated degradation
FAD	Familial AD
GCN2	General control nonderepressible-2
GSK-3β	Glycogen synthase kinase 3β
HD	Huntington's disease
HRI	Hemin-regulated inhibitor kinase
Hsp70	Heat-shock protein at 70 kDa
IP3-R	IP3 receptors
IRE1	Inositol-required 1
JNK	c-Jun N-terminal kinases
NCSTN	Nicastrin
NMDA-R	*N*-methyl-D-aspartate receptor
PEN-2 or PSENEN	Enhancer of presenilin-2
PERK	Protein kinase RNA-like ER kinase
PD	Parkinson's disease
PDI	Protein disulfide-isomerase
PKR	Double-stranded RNA-dependent protein kinase
PMDs	Protein misfolding disorders
PSEN	Presenilin
RyRs	Ryanodine receptors

SAD	Sporadic AD
UPR	Unfolded protein response
XBP1	X box-binding protein 1

Introduction

Most neurodegenerative diseases share a common feature which is characterized by the presence of abnormal protein aggregates and inclusions mainly composed of misfolded proteins. The search for common pathogenic mechanisms leading to neurodegenerative diseases has received much attention in the last decade. Parkinson's disease (PD), Huntington's disease (HD), prion-related disorders, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), and other related diseases, share transversal neuropathological events highlighting the deposition of misfolded proteins in specific regions of the central nervous system [1]. This group of pathologies are now classified as protein misfolding disorders (PMDs) [2].

A large body of literature during the last decade suggests a complex scenario wherein PMD-related protein aggregates may alter different aspects of neuronal physiology, generating major dysfunction of synapses, axonal transport, and protein degradation systems, among other pathological events [3, 4]. Several lines of evidence have underlined the importance of stress in specific subcellular organelles as a pathophysiological mechanism. Perturbations in the function of mitochondria, lysosomes/autophagy vesicles and the endoplasmic reticulum (ER) are emerging as relevant factors that drive neurodegeneration in many PMDs. In this review, we focus on the major findings relating ER stress with the etiology and progression of AD.

Many distinct alterations in the function of the ER can trigger general disturbances in protein homeostasis (also known as *proteostasis* [5]), representing an interesting target for disease intervention. The ER is a critical compartment involved in metabolic processes, such as gluconeogenesis and lipid biosynthesis, operates as a central compartment for the initiation of diverse signaling events, and represents the major intracellular calcium reservoir in the cell. One of the major functions of the ER is the synthesis and folding of proteins that traffic through the secretory pathway, which involves one third of the total proteome [6]. Disturbance of ER function is emerging as a relevant factor driving neurodegeneration in diverse neurodegenerative diseases [3], in addition to affecting the physiology of other organs including the liver, pancreas, and other tissues [7]. The mechanisms associated with ER stress in PMDs are diverse and complex and involves alterations in almost every aspect of the secretory pathway. Genetic and pharmacological manipulation of the unfolded protein response (UPR) has demonstrated a clear impact of ER stress in diseases such as HD [8], PD [9], and ALS [3] in vivo. However, despite being the most important neurodegenerative disease, functional data relating ER stress to AD are largely correlative and based mostly on studies in cell culture models. In the next section, we will summarize most relevant aspects of AD and describe the best characterized ER stress signaling pathways. Then, we will focus on discussing the major evidence linking ER stress to AD.

Alzheimer's disease, an overview

AD is the most common form of dementia and current epidemiology suggests it affects more than 25 million individuals worldwide. Aging is the major risk factor associated with development of this disease, and in the USA, AD prevalence is near 2 % of the population between the ages of 65 and 74 years. Furthermore, there is an increase of tenfold in the incidence of AD in the age group between 75 and 84 years, and near half of the population over 85 years old is affected by this disorder. There is no cure for AD, which worsens as it progresses, and eventually can lead to the death of the patient. AD is a progressive neurodegenerative disorder characterized by cognitive alterations, memory loss, and behavioral changes. This dementia is associated with synaptic impairment and loss of neurons. This is thought to be caused by the formation of neurofibrillary tangles consisting of hyperphosphorylated Tau protein and senile plaques comprising amyloid-β (Aβ) peptide in specific brain regions in association with enhanced astrogliosis, brain inflammation, and microglial proliferation [10–12].

One of the major neuropathological hallmarks of AD is the accumulation of Aβ peptide in specific brain regions such as neocortex, hippocampus and the limbic system. Progressive accumulation of Aβ peptide results in synaptic loss and neuronal death. Aβ peptide is generated by the successive proteolysis of the amyloid precursor protein (APP) by two proteases, β- and γ-secretases [13]. Mutations in three genes are linked to the development of rare familial and early forms of AD. These genes encode for APP, presenilin (PSEN) 1 and 2, and account for only 1 % of cases of AD. Other risk factors include the ε4 allele of Apolipoprotein E [14]. The mechanisms of overproduction of Aβ peptide in familial AD (FAD) cases are starting to be elucidated, but little is known about etiology of the most common sporadic forms of the disease (SAD). However, given the similarity between the clinical and histopathology observations obtained from the analysis of FAD and SAD cases, it is proposed that similar pathological mechanisms are involved in both forms of the disease.

SAD is the most common form of the disease where the production and clearance of Aβ is probably imbalanced. This promotes the accumulation of oligomeric and aggregated species of amyloid, which may trigger synaptic

dysfunction and neuronal loss. Gradual changes in the steady-state levels of Aβ peptide in the brain are thought to initiate the amyloid cascade [11, 15]. Aβ monomers are not neurotoxic; however, the local accumulation of peptides causes self-association and oligomerization generating soluble oligomers and Aβ fibrils with neurotoxic properties [16]. Aβ oligomers associate with synapses [17, 18] and alter their function; they can impair calcium homeostasis, and trigger detrimental processes such as Tau hyperphosphorylation, excitotoxicity, oxidative stress, and inflammation [14, 19, 20]. In addition, Aβ oligomers have been demonstrated to reduce synaptic plasticity and to inhibit long-term potentiation [21, 22]. The identification of FAD-related genes has allowed the generation of several mouse models of AD, which only partially recapitulate a subset of disease features [23]. This issue has been a major drawback in the field especially because most AD mouse models do not develop neuronal loss or neurofibrillary tangles. Dozens of clinical trials have been performed in the last decade with poor success, highlighting the need for a better understanding of the molecular basis of AD pathogenesis.

Mechanism of APP proteolysis, multiple components

The generation of Aβ peptide is a highly regulated and multistep process involving different components and macromolecular complexes. In this section we summarize most of the relevant components mediating the processing of APP. Aβ peptide is generated by the proteolysis of APP by β- and γ-secretases [10] (Fig. 1). The β-secretase is a transmembrane aspartate protease, also termed β-site APP cleaving enzyme-1 (BACE1) [24]. The γ-secretase is also an aspartate protease composed of at least four subunits: PSEN, nicastrin (NCSTN), anterior pharynx defective 1 (APH1), and enhancer of presenilin-2 (PEN-2 or PSENEN) [25]. The γ-secretase is an enzyme complex where the catalytic core is PSEN, a protein with eight transmembrane domains and hydrophobic loop domain located between the 6th and 7th transmembrane domain. After translation of PSEN, the hydrophobic loop is cleaved, producing an N-terminal fragment and a C-terminal fragment which are stabilized by cofactors including APH1, PEN-2, and NCSTN which form the active γ-secretase complex [26] (Fig. 1).

The generation of Aβ peptide also involves different compartments and the trafficking of APP. APP is synthesized in the ER and is N- and O-glycosylated before final movement to the plasma membrane via the Golgi apparatus. APP is found in most cell membranes and is preferentially located in the plasma membrane, where it may function in cell adhesion and cell movement. APP is also found in the Golgi apparatus membrane, mitochondria, lysosome and endosomal membrane [27]. APP processing is a highly complex and regulated process. Aβ peptide can be produced not only at the plasma membrane, but also in endosomes with subsequent release into the extracellular space [28]. APP traffics from the plasma membrane to the endosomes as part of a recycling mechanism. In the late endosomes and post-Golgi compartments, APP is probability more efficiently processed because of the acidification of these compartments, which is an optimal environment for the activity of β- and γ- secretases [29].

β-secretase cleaves APP at the N-terminal domain of Aβ peptide producing a membrane fragment called C99 and also a secreted ectodomain called sAPPβ. Subsequently, the C99 fragment is cleaved by γ-secretase to generate Aβ

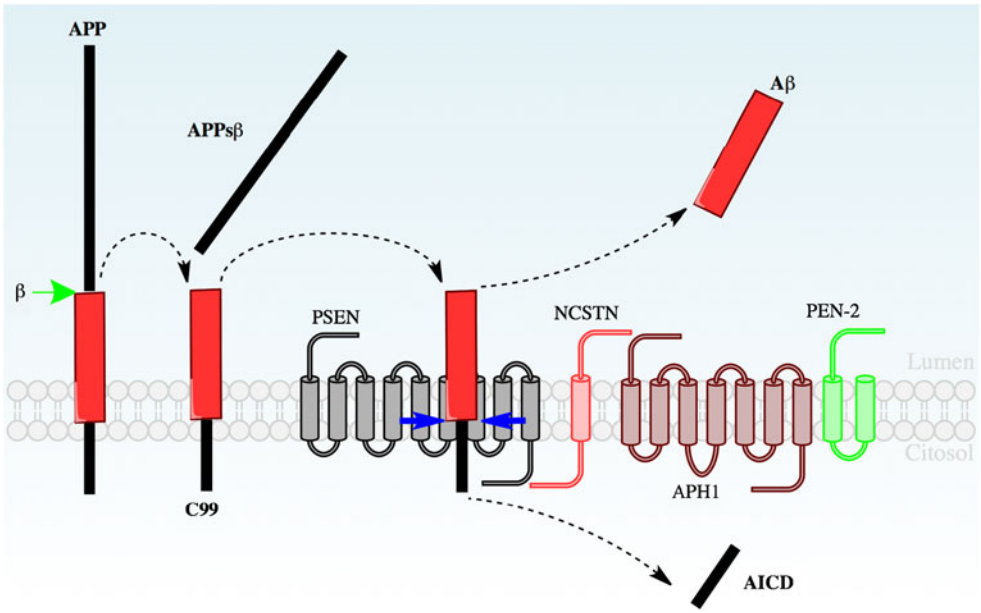

Fig. 1 APP processing. APP is cleaved by β-secretase (*β*) on the luminal side of APP generating two fragments, APPsβ and C99. The C99 fragment is cleaved by the γ-secretase in the intramembrane region to generate two fragments, the Aβ peptide (*red*) and the fragment AICD (*black*). The γ-secretase complex is composed by at least four proteins: PSEN, NCSTN, APH1, and PEN-2

peptide and another protein fragment called APP intracellular domain (AICD) [29] (Fig. 1). The cleavage by this enzyme is not precise, giving rise to Aβ peptide fragments ranging from 38 to 43 amino acids, where the peptide of 42 amino acid is the most amyloidogenic and neurotoxic [29]. Furthermore, the AICD fragment has important roles in cell signaling and could modulate the expression of APP itself.

The unfolded protein response

Although many distinct pathological events at the cellular and molecular level have been described in AD models, it remains unclear how the different pathways described so far relate to the disease. Interestingly, although very different in their nature, neurofibrillary tangles [14], neuroinflammation [30], altered calcium signaling [31], mitochondrial energy misbalance [32], exitotoxicity, and proteosomal dysfunction have been linked to the occurrence of pathological ER stress (Fig. 2) (reviewed in [29] and [33]). In addition to representing a downstream pathological mechanism, recent evidence also suggests that ER stress responses may also modulate metabolic pathways that generate Aβ. This suggests ER stress may also have a direct role in the etiology of disease (see below). Thus ER stress may be associated with a self-reinforcing cycle of amyloid production and its downstream pathogenic consequences. In this section, we summarize the key events that are triggered in cells experiencing ER stress in order to understand how these pathways link to AD.

The ER is a fundamental compartment in protein synthesis, folding and maturation. Signaling events emerging from the ER membrane are key in buffering fluctuations that affect the efficiency of protein folding. Several perturbations can alter homeostasis of the ER, leading to the accumulation of misfolded or unfolded proteins in its lumen; a cellular condition referred to as "ER stress." These alterations can include decreased ER calcium content, altered vesicular trafficking in the secretory pathway, impaired ER-associated degradation (ERAD), altered chaperone function, among other events [34]. ER stress triggers a complex network of signaling events and cellular processes that as a whole is known as the UPR [35]. The UPR orchestrates adaptation of cells to the stress associated with improper protein folding by modulating almost every aspect of the secretory pathway. Conversely, under chronic or irreversible ER stress, the UPR triggers cell death by apoptosis to eliminate damaged cells [36]. To cope with ER stress, the UPR controls the expression of genes involved in protein folding, quality control, ER and Golgi biogenesis, and protein degradation pathways. In doing so, the UPR transmits information about the protein folding status in the ER to the cytosol and nucleus, by controlling a series of specialized transcription factors [37].

ER stress stimulates at least three parallel signaling pathways initiated by the activation of the stress sensors inositol-required 1 (IRE1, α and β), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6, α and β). The IRE1α branch is the most conserved arm of the UPR. IRE1α is a kinase and endoribonuclease, that upon activation catalyzes the processing of the mRNA encoding the transcription factor X box-binding protein 1 (XBP1), removing a 26 base-pair intron [38–40]. This splicing changes the coding reading frame of the mRNA resulting in the expression spliced XBP1 (XBP1s), a potent transcription factor that regulates a subset of UPR targets [41, 42]. IRE1α also activates other signaling branches through the binding of adapter proteins such as TNFR-associated factor-2, triggering the activation of c-Jun N-terminal kinases (JNK) and apoptosis signal kinase-1 which have been implicated in processes such as autophagy and apoptosis [43]. In addition, IRE1α can degrade a subset of mRNAs and miRNAs through its RNAse domain, which can contribute to both adaptation to stress by decreasing protein translation and synthesis, or the induction of apoptosis [44–46].

Upon activation, PERK dimerizes and autotransphosphorylates, leading to the phosphorylation of eukaryotic translation initiator factor 2α (eIF2α), which arrests protein synthesis, contributing to the alleviation of the overload of proteins inside the ER [47]. In addition, phosphorylation of eIF2α allows the specific translation of the mRNA encoding activating transcription factor 4 (ATF4). ATF4 is a key transcription factor involved in the regulation of genes related to redox balance, amino acid metabolism, protein folding and apoptosis [47]. Of note, at least three additional kinases can phosphorylate eIF2α independent of ER stress including general control nonderepressible-2 (GCN2), double-stranded RNA-dependent protein kinase (PKR) and hemin-regulated inhibitor kinase (HRI) [48]. Finally, under stress conditions, the cytoplasmic tail of ATF6 is proteolyticaly processed by site-1 protease and site-2 protease in the Golgi apparatus. This releases an active cytosolic fragment (ATF6f) that operates as a bZIP transcription factor [34]. ATF6f regulates a subset of UPR target genes involved in ERAD and protein quality control [49].

Since the UPR controls both adaptation to stress and the activation of apoptosis programs in cells undergoing ER stress, it is important to define the components of the pathway that participate in both processes and that mediate the transition between them. Many different mediators of ER stress-induced cell death have been described. One of the most well characterized proteins is C/EBP-homologous protein (CHOP/GADD134), whose transcription is controlled by ATF4 [50]. The pro-apoptotic activity of CHOP involves the transcriptional upregulation of several pro-apoptotic proteins of the BCL-2 family, known as BH3-only proteins including BIM, PUMA and NOXA [51]. CHOP also

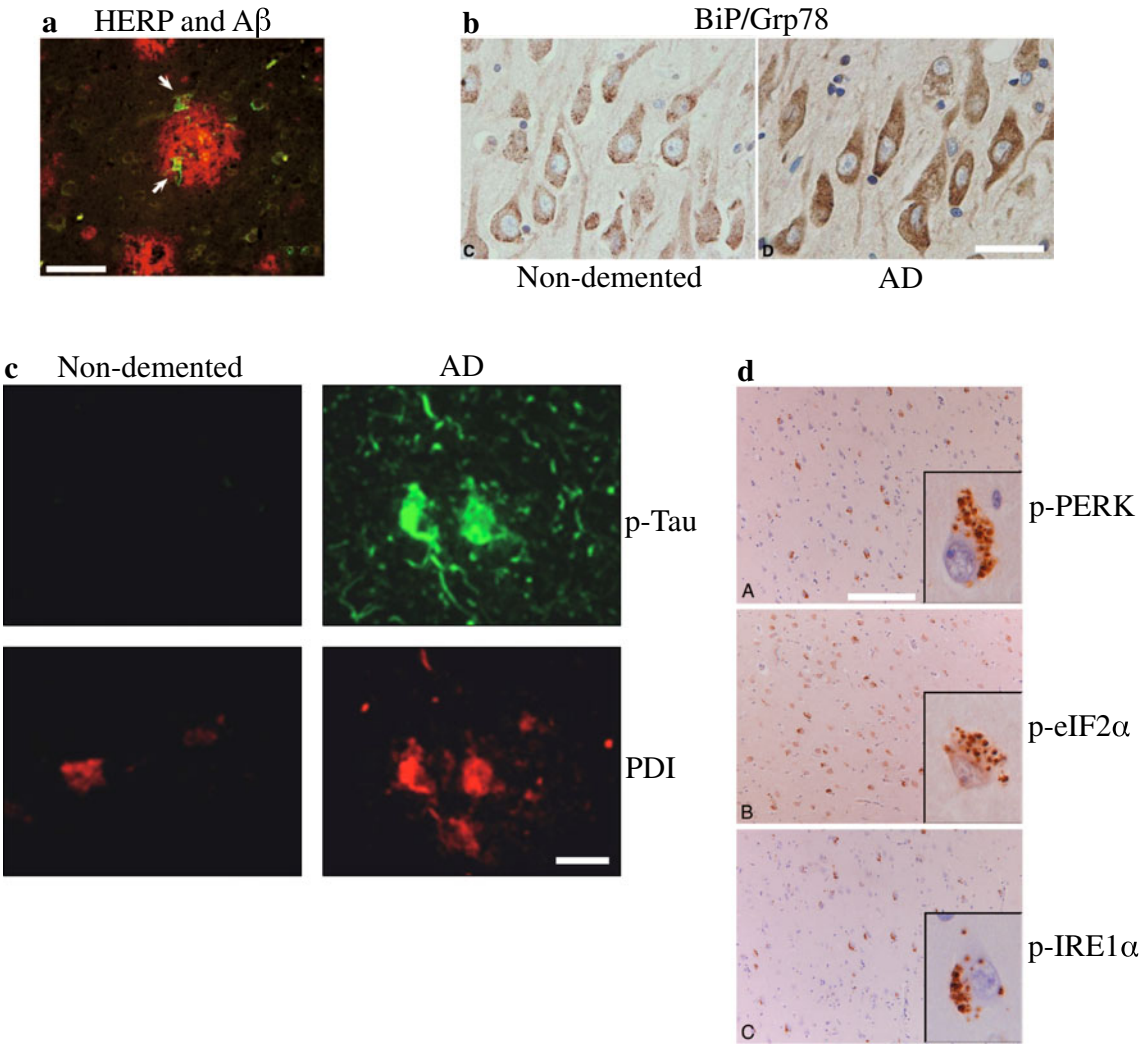

Fig. 2 Evidence implicating ER stress and UPR activation in AD pathogenesis. **a** Examples of in vivo co-localization between Aβ peptide aggregates (*red*) with HERP (*green*) in human frontal cortex tissue derived from AD patients. *Scale bar*, 50 μm. **b** BiP/Grp78 expression in AD hippocampal samples. *Scale bar*, 30 μm. **c** PDI expression and phosphorylated Tau protein are increased in cortical AD neurons. *Scale bar*, 20 μm. **d** Brain areas presenting senile plaques and neurofibrillary tangles exhibit activation of UPR sensors and regulators PERK, IRE1α and eIF2α. *Scale bars*, 200 and 20 μm for *insets*. Images were modified from Refs. [54, 58, 63, 66]. Copyright authorization was obtained from each journal

down-regulates the expression of the anti-apoptotic protein BCL-2 [52]. Expression of GADD34 may also sensitize cells to cell death since it resumes protein synthesis in stressed cells, resulting in the accumulation of misfolded proteins in the ER [50]. Many other mechanisms are involved in the induction of apoptosis by ER stress and are reviewed elsewhere (see [36, 53]).

Evidence of UPR signaling in AD

Several reports have described manifestations of ER stress in postmortem brain samples from AD patients (Fig. 2; Table 1). These studies demonstrate the occurrence of XBP1 mRNA splicing in AD temporal cortex and hippocampal tissue [54]. In addition, enhanced expression of ER chaperones including the 78-kDa glucose-related protein (BiP/Grp78), 94-kDa glucose-related protein, 70-kDa heat-shock protein (Hsp70), protein disulfide-isomerase (PDI), and/or the transcription factor CHOP in AD postmortem brain tissue [54–62]. The UPR target-gene *HERP1* participates in ERAD and is upregulated in the frontal cortex derived from AD patients, and its induction is observed in brain areas containing amyloid plaques [63]. Moreover, the phosphorylation of the UPR stress sensor PERK and its downstream substrate eIF2α are observed in the brains of AD patients [64–67] (Fig. 2). Likewise, the activation of a related kinase PKR correlates with ER stress levels in brain of AD-derived samples [68].

Table 1 Evidence linking ER stress to AD

Component	Human samples	Animal models	In vitro models
PERK/eIF2α	Increase phosphorylation of PERK and eIF2α in AD brains [64, 65, 67]	Increased eIF2α phosphorylation in 5XFAD mouse model [64]	eIF2α phosphorylation in cells treated with Aβ [98, 111] Knock-down of PERK enhances Aβ toxicity [113] PSEN1 mutation inhibits activation of PERK [82, 84] eIF2α phosphorylation in cell overexpressing APP with E693Δ mutation [95]
ATF4			ATF4 regulates the activity of γ-secretase [120, 121]
IRE1α			PSEN1 mutation inhibits IRE1α activation [84]
XBP1	Nonconvetional XBP1 splicing in temporal cortex of AD brains [54] XBP1 promoter polymorphism is associated with risk to develop AD [130]	Protective role of XBP1s in flies overexpressing Aβ [101] Knock-down of XBP1 enhances neurotoxicity on a fly model of taupathies [76]	XBP1 splicing upon treatment with Aβ [101, 102, 112] Protective role of XBP1s in PC12 treated with oligomeric Aβ [101] XBP1s binds to the promoter region of AD-related genes [42]
ATF6			PSEN1 mutation inhibits activation of ATF6 [84]
CHOP	CHOP is upregulated in the temporal cortex of AD brains [54]	CHOP is unaltered in Tg2576 AD mouse model [54] Enhanced expression of CHOP in a rabbit model of Aβ toxicity [114].	AICD associates with promoter region of CHOP gene [118] Increased CHOP expression in cells treated with Aβ [97, 113]
BiP/GRP78	Increased BiP in cytologically normal neurons [59] and associated with amyloid deposits [55] in AD brains Unaltered BiP expression in temporal cortex of AD brains [54]	Enhanced expression of BiP in a rabbit and mouse model of Aβ toxicity [103, 114] BiP expression is unaltered on Tg2576 mouse model of AD [54]	Unaltered BiP expression in fibroblast from FAD-linked PSEN1 mutation [81] and null mutant [84] Activation of BiP upon treatments with Aβ peptide [98–100, 106, 107, 113] Enhanced expression of BiP in cell lines and induced pluripotent stem cells expressing APP with E693Δ mutation [95, 105] ER stress triggers the binding of BiP to APP [60, 85]
PDI	Decrease PDI activity by S-nitrosylation in sporadic AD brains [128] PDI is increased in neurons and inclusions of temporal cortex of AD brains [54, 61] PDI interacts with Aβ in cerebrospinal fluid [141]	PDI expression is unaltered in Tg2576 mice [54] Pharmacological activation of PDI improves AD in 5XFAD mice [142]	Unaltered PDI in fibroblasts expressing FAD-linked PSEN1 mutation [81]
Others components	HSP72 is increased surrounding neuritic plaques and neurofibrillary tangles from AD brains [59]		HRD1 is involved in the degradation of APP [56]

Interconnection between ER stress and Tau pathology

Neurons contain Tau protein, which serves to stabilize microtubules. Neurodegeneration associated with tauopathies, such as AD and frontotemporal dementias, are characterized by the presence of intraneuronal inclusions containing hyperphosphorylated Tau [69]. ER stress markers are observed in neurons and glia exhibiting Tau pathology [70]. IRE1α and PERK phosphorylation were described in patients affected with AD and as well as a wide range of frontotemporal dementias [69]. In vitro studies suggest that the induction of ER stress by the exposure of cells to Aβ oligomers correlates with the induction of Tau phosphorylation [71], placing ER stress as an interesting connection between Aβ-mediated neurotoxicity and Tau hyperphosphorylation [72].

It has been suggested that phosphorylation of Tau is unable to trigger ER stress and thus an UPR. Conversely, stimulation of UPR signaling can induce Tau phosphorylation [73], possibly through the activation of glycogen synthase kinase 3β (GSK-3β) [74]. Interestingly, neurons exhibiting activated PERK co-express active GSK-3β in affected neurons of AD brain [66]. More importantly, genetic variants associated with single nucleotide polymorphisms in the *PERK* gene have been suggested to represent a risk factor for the development of sporadic tauopathies [75]. An elegant study has shown that decreasing XBP1 expression enhances the neurotoxicity induced by overexpression of human Tau protein in a fly model of tauopathies, suggesting a functional connection between the UPR and Tau in vivo [76]. This fly model recapitulates many aspects of Tau-related neurodegeneration, including age-dependent degeneration, oxidative stress, and apoptotic neuronal loss, in addition to the activation of XBP1 mRNA splicing in affected neurons [76].

A function for PSEN in the ER stress response?

Accumulating evidence suggest that PSEN participates in the maintenance of calcium homeostasis in the ER and cytosol. In addition, a few studies indicate that PSEN may also affect the susceptibility of cells to ER stress. However, the mechanistic relationship between the UPR and PSEN function is unclear [77]. Two studies have shown that PSEN deficiency results in delayed activation of PERK and IRE1α signaling, as well as a reduction in the proteolytic processing of ATF6 under ER stress conditions [78, 79]. However, in other studies, the levels of BiP/Grp78 and CHOP where observed to be unaltered in PSEN-deficient cells undergoing ER stress [80, 81]. In contrast, the overexpression of the AD-associated mutant of PSEN alters the activation of the UPR in different experimental systems [81–86].

PSEN regulation of the UPR may have functional consequences for cell viability. For example, cortical neurons that are transgenic for mutant PSEN are more sensitive to ER stress [83, 87]. These cells also exhibit altered translational regulation mediated by PERK signaling [82]. Expression of mutant PSEN increases calcium release from the ER, enhancing the sensitivity of cells to ER stress-mediated apoptosis [77]. PSEN has been detected in complex with the ER calcium ATPase SERCA and with other ER-resident calcium channels (i.e., IP3 receptors (IP3-R) and ryanodine receptors (RyRs)) which contribute to the effects of mutant PSEN on ER dysfunction [86, 88, 89]. PSEN was also suggested to modulate IRE1α cleavage and release of its cytosolic domain [78]. Although the link between PSEN and UPR activation is well described, the precise mechanisms governing this interconnection remains to be elucidated.

ER stress as a driver for neuronal cell loss in AD

Several reports have claimed a function for ER stress-mediated apoptosis in response to Aβ peptide (Fig. 3) (reviewed in Ref. [90]). More than a decade ago, a pioneer study in the UPR field found that treatment of cells with Aβ peptides leads to the activation of an ER-specific caspase (caspase-12 in mice and possibly caspase-4 in humans), that correlates with the induction of apoptotic cell death [91]; a finding which has been confirmed by other groups [92, 93]. Although processing of caspase-12 is an accepted marker of ER stress, its functional contribution to apoptosis is debated [94], and it may operate in pro-inflammatory pathways.

Several studies have demonstrated that exposure of cells to Aβ oligomers or fibrils in different experimental models, such as cell lines, primary neuronal cultures, or organotypic hippocampal brain slices, trigger ER stress [90, 95–103]. For example, evidence has been provided for the activation of eIF2α and PERK phosphorylation, XBP1 mRNA splicing, and upregulation of CHOP and several ER chaperones in such studies. The effects of Aβ peptide in the function of the ER may be indirect since treatment of primary neuronal cultures with Aβ induces the collapse of microtubules that ultimately affects the dynamic architecture of the ER [98]. Similar correlations have been shown in transgenic animal models of AD and brain samples derived from AD patients [104]. Remarkably, a recent report detected the spontaneous induction of ER stress (BiP/Grp78 and Caspase-4) in neuronal cultures derived from induced pluripotent stem cell from sporadic and familial AD cases [105]. In this new model of AD, intracellular accumulation of Aβ oligomers was observed, and treatment of cells with antioxidants reduced the ER stress response of AD-neuronal cells.

Additional associations between Aβ, ER stress and cell death are proposed through free-radical oxygen species and mitochondrial dysfunction [99, 106–108] (reviewed in Ref. [109]). A recent report also demonstrates that Aβ oligomers can induce ER stress through a *N*-methyl-D-aspartate

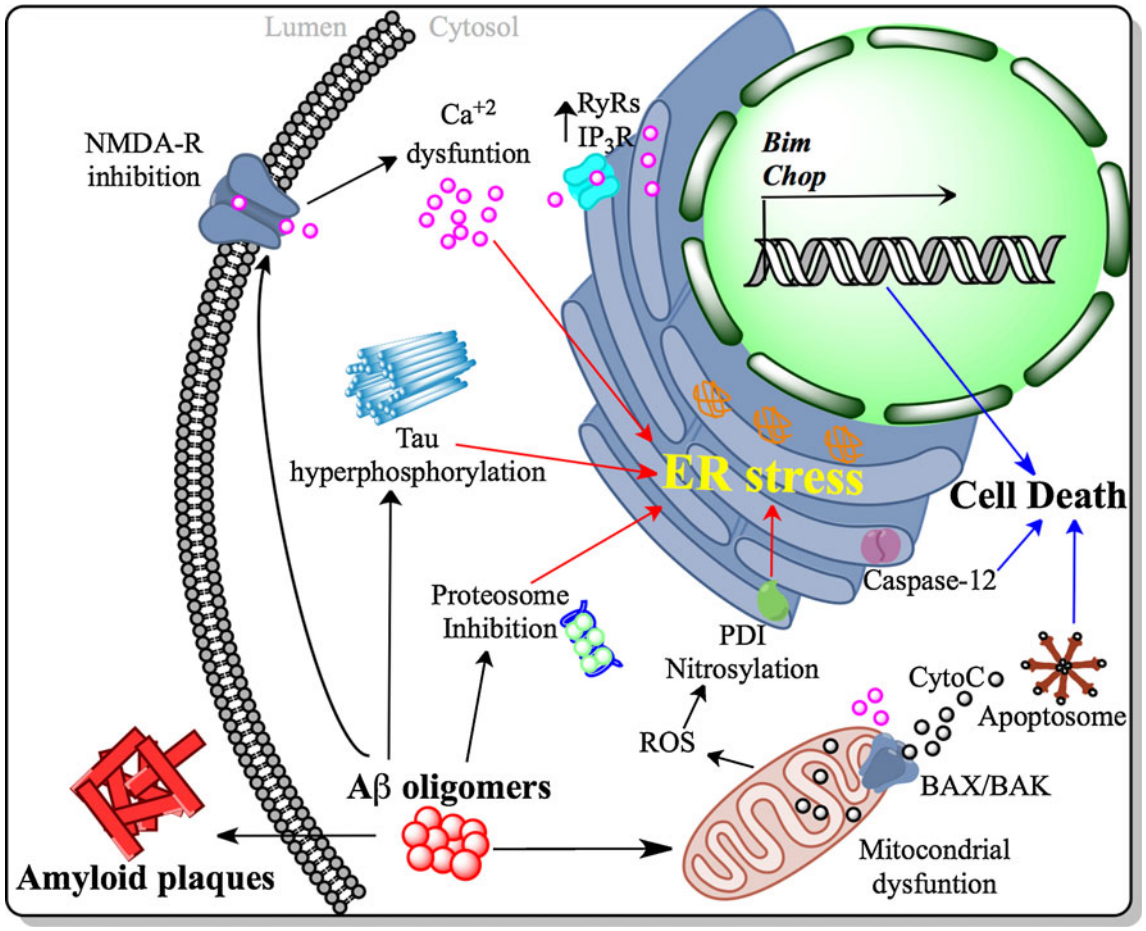

Fig. 3 ER stress-mediated cell death in AD models. Aβ peptide aggregates engage and inhibit NMDA-R, causing an influx of calcium into the cytoplasm. In addition, change in levels of IP3-R and RyRs channels can also alter calcium homeostasis and trigger cell death through the mitochondrial apoptosis pathway (apoptosome dependent). Mitochondrial dysfunction may also trigger the generation of oxidative stress, which may impact the ER by altering PDI function. All these cellular events can generate chronic ER stress leading to the activation of pro-apoptotic events controlled by the UPR including the upregulation of BIM and CHOP

receptor (NMDA-R)-dependent mechanism which involves GluN2A and GluN2B receptor subunits [94]. In this model, NMDA-R alterations trigger an imbalance in cytosolic calcium which stimulates excessive reactive oxygen species and, as a consequence, ER stress-mediated cell death [94]. Finally, a recent report also suggested that Aβ oligomers also trigger an ER stress response in astrocytes both in vitro and in mouse models of AD, associated with altered calcium signaling and astrogliosis [103]. Many other reports have linked calcium disturbances and ER stress in cellular models of Aβ neurotoxicity (reviewed in [103, 110]).

It is still a mater of debate whether or not ER stress is a consistent signature of Aβ-mediated responses. For example, some groups have reported that treatment of cells with extracellular Aβ peptide does not induce ER stress, as measured by XBP1 mRNA splicing, PERK phosphorylation, or by monitoring CHOP expression in cortical primary cultures [111]. Furthermore, in another study the treatment of a neuronal cell line with Aβ caused only "mild" ER stress [112]. Another study suggested that the selective activation of PERK, and not IRE1α/XBP1 signaling, is an early event triggered by Aβ peptide [113]. In this study PERK was demonstrated to have a function as a protective factor, controlling the expression of BiP/Grp78 which functioned in the attenuation of apoptosis by cells exposed to Aβ peptide aggregates [113].

The E693Δ mutation in APP localizes within the Aβ sequence and is observed in some Japanese pedigrees affected by AD [95]. This mutation leads to a marked reduction in Aβ peptide secretion, leading to enhanced oligomerization of Aβ peptide but not its fibrillization [95]. The E693Δ mutation affects the trafficking of APP and causes ER stress and Golgi apparatus dysfunction possibly due to intracellular Aβ oligomerization [95, 105]. In contrast, using a neuroblastoma cell line that produces endogenous Aβ peptide it was shown that ER stress is not induced at basal levels [97]. However, when the cells are challenged with an ER stress agent, these E693Δ expressing cells are hypersensitive to ER stress-mediated toxicity and

exacerbated UPR signaling [97]. Similarly, a potentiation in neurotoxicity between Aβ peptide and exogenous ER stress stimulation (pharmacological induction) is observed in other systems using organotypic hippocampal slice cultures [96].

In animal models of AD, the neurotoxicity of Aβ has also been correlated with the occurrence of ER stress. Ectopic expression of spliced XBP1 protects neuronal cells against the overexpression of Aβ peptide in a model of AD in *Drosophila melanogaster* [101]. In this study, XBP1s was shown to directly regulate ER calcium homeostasis by downregulating RyR expression [101]. This work showed for first time a direct functional relationship between the UPR and AD in vivo [101]. Other correlative studies in a rabbit model of AD indicated that ER stress is induced by the hippocampal injection of Aβ [114]. The glial cell line-derived neurotrophic factor was identified as a protective factor against the intra-brain injection of Aβ, which also attenuated ER stress levels [114]. A functional study in the an AD mouse model expressing mutant APP (Tg2576 mice) demonstrated that treatment of animals with the chemical chaperone 4-PBA decreased ER stress levels and alleviated the pathology [115]. In contrast, another study using Tg2576 transgenic mice showed no signs of UPR activation, although ER stress markers were confirmed in human AD samples [54]. 5XFAD transgenic mice containing mutations in APP and PSEN1, exhibit signs of ER stress including the presence of phosphorylated eIF2α and JNK [64, 116]. Remarkably, depletion of JNK activity improves memory defects, neuronal viability and reduces the content of amyloid plaques in the brain in models of AD [116]. In contrast, a recent study suggested that Aβ peptide may also induce the hyperactivation of the sodium and calcium exchanger NCX3, increasing ER calcium levels, delaying apoptosis responses [117]. Thus, all these in vivo studies highlight the need for generating more understanding in this area in order to define the actual contribution of ER stress to different aspects of AD pathogenesis.

APP may also operate as a regulator of ER stress-mediated apoptosis responses. Mechanistic analysis of the AICD has revealed that it can promote CHOP transcription and may enhance cell death after treatment of cells with an ER stress-inducing agent [118]. Interestingly, this mechanism is dependent on γ-secretase activity release of AICD. However, this model is widely debated in the literature [118, 119]. Overall, very little validation is available in linking ER stress to AD in vivo through genetic or pharmacological manipulation of the UPR, and most of the studies available so far are correlative. The mechanisms explaining how Aβ peptide triggers ER stress/UPR activation and what is the exact consequence of this particular process to neuronal loss and cognitive dysfunction in AD still remains an important open question.

The UPR as component of the etiology of AD

Accumulating evidence suggests that UPR signaling events may actually control the expression of diverse AD-related proteins (Fig. 4). For example, Vassar and collaborators demonstrated a direct regulation of BACE1 translation by eIF2α [64], wherein amyloidogenesis is enhance by this pathway [64]. Furthermore, ER stress increases the activity of γ-secretase through ATF4 [120, 121]. Under ER stress conditions, ATF4 promotes the transcription of PSEN gene, a component of γ-secretase [120].

In an effort to define the universe of XBP1s-target genes, a genome-wide screening using a chromatin immunoprecipitation-on-chip strategy identified a regulatory network governed by XBP1 involving a subset of major AD-related genes [42] (Fig. 4). In this work, in addition to identifying classical XBP1s target genes involved in ER stress mitigation, unexpected targets were identified including genes encoding for (1) γ-secretase components (PSEN1, NCSN, and PEN-2), (2) proteins involved in APP trafficking and processing (UBQLN1, MINT3, and FE65-3), (3) a chaperone-regulator linked with neurodegenerative diseases (BAP/Sil1), (4) ERAD components modulating APP degradation (HERP1), and (5) two candidate genes that may contribute to Tau phosphorylation (cyclin-dependent kinase 5, Cdk5 and Cdk5rap3) [42]. Although this study places XBP1s as possible master modulator of a full cluster of genes related to AD, no functional studies are available to validate this model, and so far with the data available, it is not possible to predict what is the effect of XBP1 in gene expression (positive or negative) or the downstream consequences of this regulation in terms of Aβ peptide production.

Data are also available suggesting that UPR signaling events could control early steps of APP maturation and processing. For example, altered processing and subcellular distribution of APP has been observed in cells undergoing ER stress [122]. APP can redistribute from late to early compartments of the secretory pathway thus reducing Aβ peptide secretion as a result of interactions with the ER chaperone BiP/Grp78 [85]. This interaction may alter APP maturation and processing, and the enzymatic reactions associated with secretases in late secretory compartments, such as the Golgi apparatus and endo-lysosomal system [85]. In addition, Aβ peptide production has been suggested to occur in the ER [123]. Like many other proteins produced through the secretory pathway, APP is susceptible to misfolding in the ER, resulting in targeting to the ERAD [124]. HRD1 is a specific UPR target gene that regulates degradation of APP in steady-state conditions through ERAD pathways [56]. HRD1 also modifies the metabolism and processing of APP to generate Aβ peptide in a mechanism that is dependent on ATF6 and XBP1 through the upregulation of HRD1 expression [56].

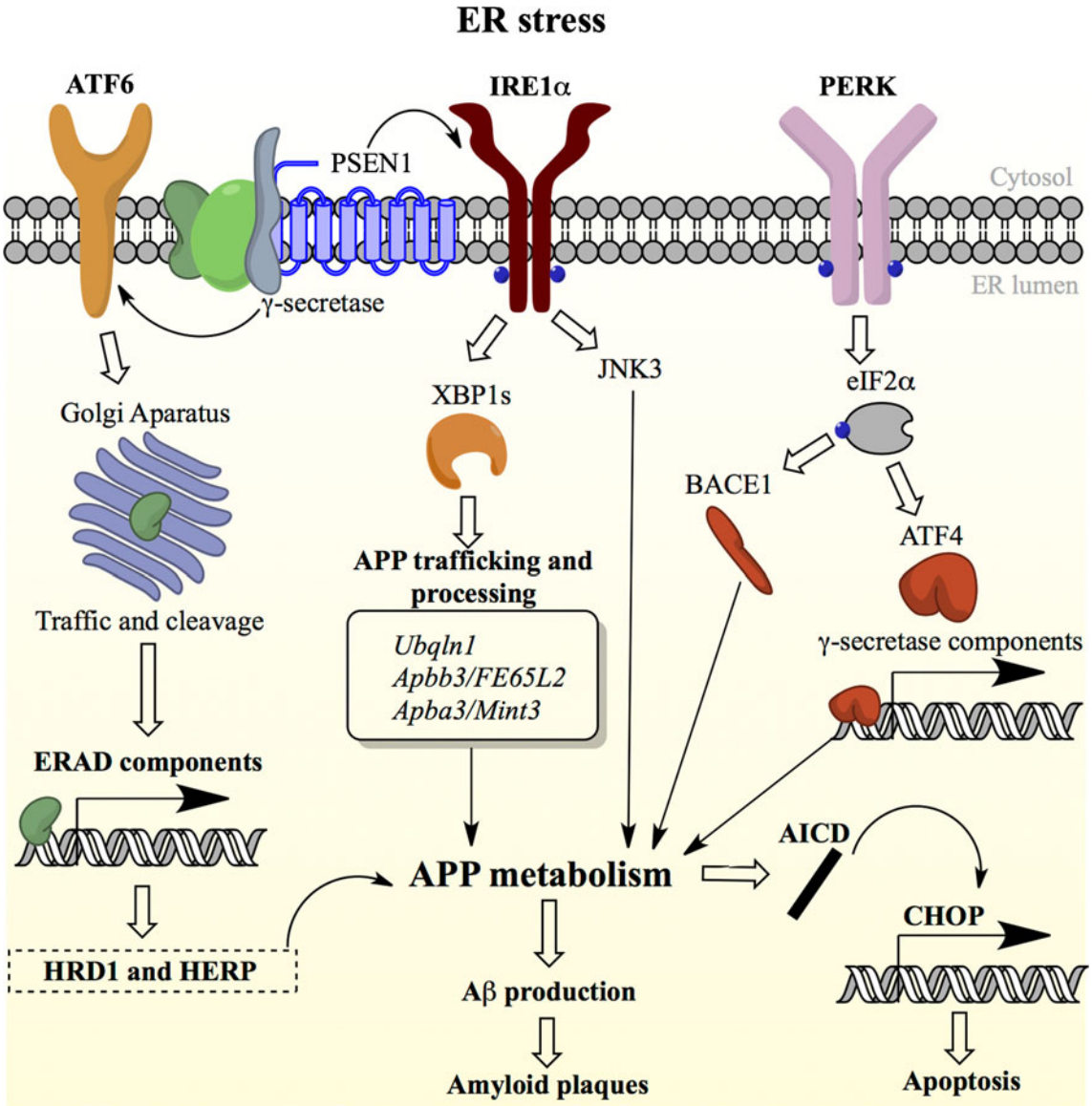

Fig. 4 Modulation of AD-related genes by the UPR. Distinct UPR signaling events have been shown to affect the expression of AD-related genes and also alter the processing of APP. ATF6 traffics to the Golgi apparatus and cleaved to stimulate the transcription of ERAD components like HRD1 and HERP1. Also, ATF6 and IRE1α cleavage could be modulated by PSEN. XBP1 transcription factor binds to putative targets involved in APP trafficking and degradation. PERK can also promote translation of BACE1 and transcription of γ-secretase component. JNK3 may also modulate APP processing under ER stress conditions. All of these pathways are modulated by ER stress, affecting APP metabolism and Aβ peptide production. In addition, AICD acts as a transcription factor that binds the CHOP promoter

Cdk5 also phosphorylates APP affecting its processing and metabolism, and the cleavage of Cdk5 activator p35 to p25 by calpain is involved in neuronal loss in certain models of AD (reviewed in Ref. [125]). ER stress can activate Cdk5 contributing to the induction of apoptosis [126]. A recent study provided evidence suggesting the occurrence of a general translational block in animal models of AD and possibly in human postmortem brains involving the mTOR pathway [116]. Of note, this process generates ER stress which is associated with JNK3 activation [116] and phosphorylation of APP, which facilitates its amyloidogenic processing [116].

Other components of the ER machinery may represent primary targets of AD pathogenesis. PDI is an ER foldase and chaperone that assists the formation of disulfide bonds in the early synthesis of proteins in the ER [127]. The S-nitrosylation of PDI has been observed in brain samples derived from sporadic forms of AD. S-nitrosylation of PDI inhibits it enzymatic activity triggering ER stress [128]. Thus, the generation of oxidative stress in AD brain may be a direct cause of ER stress in this disease by disrupting the protein folding process. PDI has also been suggested to induce neuronal loss in AD models since a high throughput

pharmacological screen identified PDI inhibitors as powerful compounds that decrease neurodegeneration in models of AD, and also HD [129]. In this study it was suggested that PDI, and also its orthologue ERp57, may trigger a mitochondrial apoptosis pathway. Many other studies have linked PDI family members to neurodegeneration in diverse diseases (reviewed in [127]). Together, these findings suggest that improper PDI function (either increased or decreased) may contribute to neurodegeneration.

Remarkably, a recent report demonstrated for the first time a genetic association between alteration in UPR components and AD. The 116C/G polymorphism in the *XBP1* promoter was associated with risk to develop AD in the Chinese population [130]. Moreover, the genotypes −116CG and −116GG were significantly associated with increased AD risk in females, and in conjunction with the APOE ϵ4 a strong cognitive impairment was observed. This polymorphism was initially identified as a risk factor to develop bipolar disorders [131] and later on linked to schizophrenia in the Japanese population [132] and personality alterations in woman [133]. In vitro experiments demonstrated that this polymorphism reduces the expression of XBP1s, having a functional consequence on downstream UPR responses [131]. In contrast, this polymorphism was not associated with bipolar disorders in the Chinese population [134] or in subjects with European origin [135]. So far, no studies have investigated the possible role of the UPR in cognition and memory-related processes. Of note, phosphorylation of eIF2α and expression of ATF4 have been linked to learning and memory through kinases not related to ER stress [136–138], suggesting that fine-tuning of ER protein homeostasis is a relevant contributor to cognitive processes. It remains to be determined what is the actual contribution of XBP1 to AD.

In summary, increasing evidence suggests the existence of a complex regulatory network wherein the UPR modulates essential molecular events involved in the etiology of AD. Additional integrative and functional studies are necessary to define the actual contribution of the UPR network to AD pathogenesis.

Conclusions

In this article, we have reviewed the relevant evidence supporting a connection between ER stress and AD (Table 1). Most of the data available are based on cellular models of AD where ER stress is proposed to operate as a relevant factor driving neuronal degeneration. In contrast, a few recent studies also suggest that ER stress may actually modulate the expression of a full network of genes involved in APP processing and the generation of Aβ peptide. More importantly, the recently identified association between an XBP1 polymorphism and the development of AD suggests a causal role of ER stress in the etiology of the disease. However, most of data available lack functional testing necessary to define the actual impact of ER stress on AD in vivo. Only a few studies have manipulated the UPR in animal models of AD. It is clear that more research is needed to solve this relevant question and move forward in defining novel targets for disease intervention. It is striking to notice that the field of ER stress and neurodegeneration has moved much faster in other less frequent diseases such as HD, ALS, spinal cord injury, and PD, where solid evidence has defined a functional impact of ER stress in disease pathogenesis (reviewed in [3, 8, 9, 139]). Part of the difficulty in the AD field is the lack of solid animal models that recapitulate the integral aspects of the human pathology. In recent years many novel pharmacological modulators and genetic strategies (mouse models and gene therapy tools) have been made available to manipulate the UPR in a disease context [6, 140]. We believe these resources are going to provide important clues in the near future about the actual impact of ER stress on AD, the most prevalent neurodegenerative disease in the human population.

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