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STATE-OF-THE-ART REVIEW

Emerging roles of ER stress in the etiology and pathogenesis of Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by synaptic dysfunction and accumulation of abnormal aggregates formed by amyloid-β peptides or phosphorylated tau proteins. Accumulating evidence suggests that alterations in the buffering capacity of the proteostasis network are a salient feature of AD. The endoplasmic reticulum (ER) is the main compartment involved in protein folding and secretion and is drastically affected in AD neurons. ER stress triggers the activation of the unfolded protein response (UPR), a signal transduction pathway that enforces adaptive programs to recover homeostasis or trigger apoptosis of irreversibly damaged cells. Experimental manipulation of specific UPR signaling modules in preclinical models of AD has revealed a key role of this pathway in regulating protein misfolding and neurodegeneration. Recent studies suggest that the UPR also influences synaptic plasticity and memory through ER stress-independent mechanisms. Consequently, targeting of the UPR in AD is emerging as an interesting therapeutic approach to modify the two pillars of AD, protein misfolding and synaptic failure. Here, we review the functional role of ER stress signaling in AD, discussing the complex involvement of the pathway in controlling neuronal survival, the amyloid cascade, neurodegeneration and synaptic function. Recent intervention efforts to target the UPR with pharmacological and gene therapy strategies are also discussed.

Introduction

Alterations in the maintenance of proteostasis are considered a common feature in various neurodegenerative diseases. Parkinson's disease, amyotrophic lateral sclerosis, Huntington's diseases, prion-related disorders, and Alzheimer's disease (AD) are all characterized by a long clinically silent phase, where abnormal

Abbreviations
AD, Alzheimer's disease; APP, amyloid precursor protein; ASK1, apoptosis signal-regulating kinase 1; ATF, activating transcription factor; Aβ, amyloid-β; Aβo, amyloid-β oligomers; BACE1, β-APP cleaving enzyme 1; BCL-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CHOP, C/EBP homologous protein (CHOP); CREB, cAMP response element-binding protein; eIF2α, eukaryotic initiation factor 2α; ERAD, endoplasmic reticulum-associated degradation; ER, endoplasmic reticulum; FAD, familial Alzheimer's disease; IRE1, inositol requiring enzyme-1; ISRIB, integrated stress response inhibitor; JNK, c-Jun N-terminal kinase; KIRA, kinase inhibiting RNAse attenuator; NF-κB, nuclear factor-κB; NMDA-R, *N*-methyl-D-aspartate receptor; PDI, protein disulfide isomerase; PERK, protein kinase R-like endoplasmic reticulum kinase; PMD, protein misfolding disorder; p-tau, phosphorylated tau; RIDD, regulated IRE1-dependent decay; UPR, unfolded protein response; XBP1/s, X-box binding protein 1/spliced form.

proteins accumulate and aggregate in the brain, leading to altered synaptic function and eventually neuronal loss [1]. This group of diseases is now classified as protein misfolding disorders (PMDs) and they include a variety of conditions affecting the central and peripheral nervous systems [2]. AD is the most common form of dementia and affects more than 25 million individuals worldwide. Its incidence progresses with age and nearly half of the population over 85 years old is affected by this disorder or other related dementias. There is no cure for AD, which worsens as it progresses, leading eventually to the death of the patient on average 10 years after diagnosis. The main histopathological features of AD are the formation of neurofibrillary tangles, constituted of hyperphosphorylated tau proteins, and senile plaques comprising amyloid-β (Aβ) peptides [3]. The accumulation of Aβ oligomers and amyloid plaques in specific brain regions is associated with enhanced brain inflammation and abnormal glial activation [4]. Aβ peptides are generated through the cleavage of the amyloid precursor protein (APP) after a sequential processing by the β-secretase (β-APP cleaving enzyme 1; BACE1) and γ-secretase enzymes [5–7]. Aβ peptides form extracellular insoluble plaques, fibrils or soluble and diffusible oligomers that are described as highly neurotoxic [3]. Tau normally functions in stabilizing neuronal microtubules. Phosphorylated tau (p-tau) loses its function and aggregates into intracellular neurofibrillary tangles [8,9]. Both lesions are observed in rare familial AD cases (FAD) in addition to the common sporadic form representing 90–95% of total cases. Interestingly, genetic variants linked to FAD enhance Aβ production, involving direct mutations in the genes encoding APP or the γ-secretase catalytic components presenilin 1 and 2 [10]. Those mutations increase the quantity of the most aggregation-prone Aβ peptide subtype, $A\beta_{1-42}$, associated with an early onset and aggressive form of AD [3,11]. While the Aβ peptide acquires neurotoxic properties depending on its concentration, structural features and localization, its production is normally observed at a young age and it could also exert a beneficial effect on neuronal plasticity at physiological levels [12,13].

To maintain proteostasis – the balance between protein synthesis, degradation and any post-translational processing – cells dispose of a complex array of sensors and transcriptional effectors [14]. Aging is the main risk factor to develop AD and is associated with a gradual decay of the buffering capacity of the proteostasis network [15]. During normal aging, oxidized proteins and abnormally ubiquitinated proteins often accumulate, a phenomenon exacerbated in the AD brain [16–18]. Additionally, the major organelle involved in protein folding and quality control, the endoplasmic reticulum (ER), is dramatically affected in AD neurons (see below). If misfolded proteins accumulate within the ER lumen, exceeding the capacity of the protein-folding machinery, the unfolded protein response (UPR) is activated to restore proteostasis [19]. However, under chronic or irreversible ER stress, the UPR shifts its signaling toward a proapoptotic program [20,21]. During AD, the continuous accumulation of Aβ or p-tau is proposed to result in abnormal levels of ER stress, contributing to synapse dysfunction and neurodegeneration [22]. In the past 10 years, accumulating evidence supports a therapeutic potential of targeting the UPR to slow down AD in various preclinical models using pharmacological or gene therapy approaches [23–25]. In this review, we discuss the latest discoveries highlighting the functional role of ER stress in AD and its impact in synaptic dysfunction and cognitive impairment. Novel perspectives for future therapeutic interventions and current challenges are also discussed.

The unfolded protein response

Abnormal levels of misfolded proteins at the ER engage the UPR, a complex signaling process initiated by the activation of a set of stress transducers that enforce a quick response to improve cell function (Fig. 1) [26,27]. ER stress sensors include protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1α (IRE1α, referred to as IRE1 here) and β, and activating transcription factor (ATF) 6α and β. At basal level, the luminal domain of those sensors interacts with the ER-resident chaperone Grp78/BiP, preventing their activation [28]. While initially linked to calcium imbalance and protein misfolding at the ER lumen, UPR activation is also sensitive to different cytoplasmic alterations, including a defect in autophagy, oxidative stress, proteasome inhibition, and metabolic or mitochondrial dysfunctions [19,20]. Importantly, most of those alterations are also part of AD physiopathology [29–33].

PERK is a type-I transmembrane kinase located at the ER membrane. PERK activation allows a direct inhibition of protein synthesis through the phosphorylation of the protein translation factor eukaryotic initiation factor 2α (eIF2α) (Fig. 1) [34]. However, under eIF2α phosphorylation some usually poorly translated mRNAs containing multiple upstream open reading frames are translated at a higher rates [35], including ATF4. ATF4 is a transcription factor that controls redox homeostasis in the ER, amino acid biosynthesis,

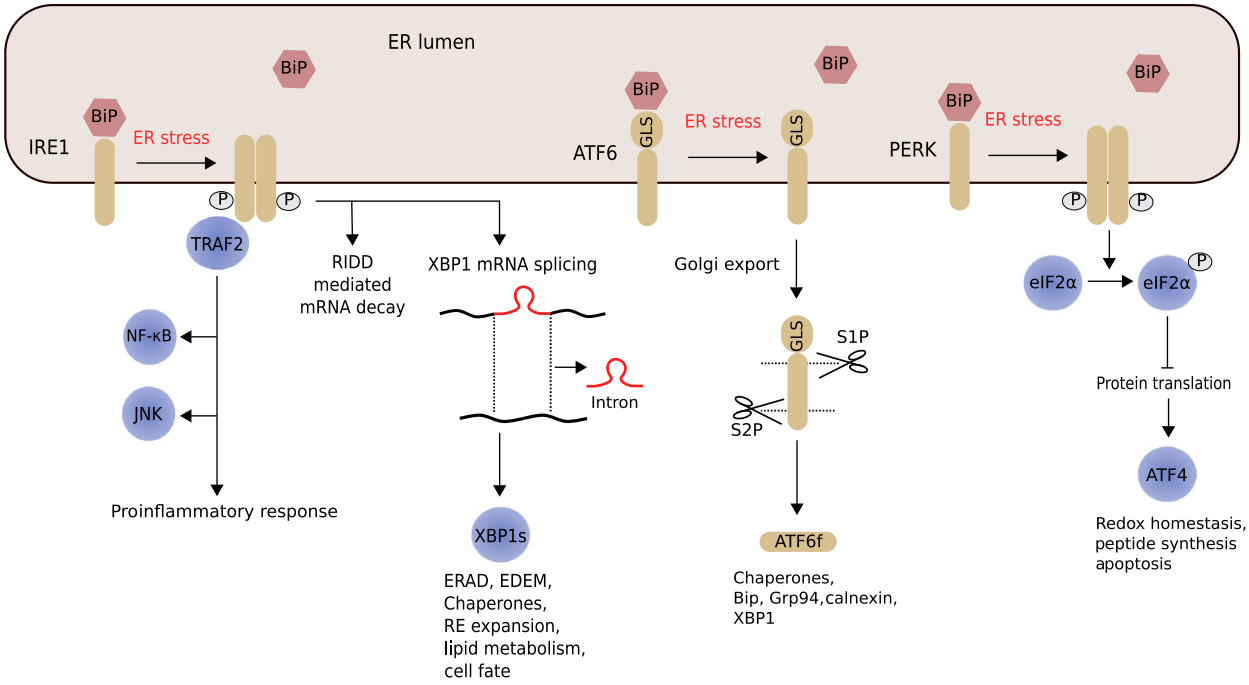

Fig. 1. The unfolded protein response (UPR) signaling. ER stress induces an adaptive response known as the UPR. Three major stress sensors control UPR-dependent responses, namely IRE1, PERK, and ATF6. These ER-transmembrane proteins transduce signals to the cytosol and nucleus to restore protein-folding capacity. IRE1 RNase activity processes the mRNA encoding the transcription factor XBP1, leading to the expression of an active transcription factor that upregulates a subset of UPR-target genes related to folding, ERAD, protein quality control and organelle biogenesis. IRE1 degrades select mRNAs and activates JNK and NF-κB pathways through binding to adapter proteins. ATF6 is localized at the ER at basal conditions and contains a bZIP transcriptional factor in its cytosolic domain. In cells undergoing ER stress, BiP is released which unmask a Golgi localization signal (GLS), allowing ATF6 translocation to the Golgi apparatus where it is processed by site 1 and 2 proteases, releasing its cytosolic domain (ATF6f). ATF6f controls upregulation of select UPR-target genes. Activation of PERK attenuates general protein synthesis through phosphorylation of the initiation factor eIF2α. eIF2α phosphorylation allows the selective translation of ATF4 mRNA, which encodes a transcription factor that induces the expression of genes involved in antioxidant responses, amino acid metabolism, and apoptosis.

autophagy and protein folding, but also cell fate through the induction of the proapoptotic factor C/EBP homologous protein (CHOP) and members of the B-cell lymphoma 2 (BCL-2) protein family [36–38]. CHOP can also decrease the phosphorylation level of eIF2α through the induction of the phosphatase growth arrest and DNA damage-inducible protein 34 (GADD34) and reverse the global translation inhibition state of the cell, producing abnormal levels of reactive oxygen species [39,40]. Pharmacological modulators of PERK are currently under development considering its major involvement in cancer and neurodegenerative diseases [41,42]. Small molecules affecting PERK/ATF4 signaling include inhibitors of the phosphatases controlling eIF2α (constitutive and ER stress inducible [43]), such as salubrinal, guanabenz, and sephin, which all prolong the effects of the protein translation blockade [44–46]. In addition, a drug activating PERK, CCT020312, is able to stimulate its kinase domain without affecting other UPR stress sensors [47]. A selective PERK kinase inhibitor, GSK2656157, has also been developed and tested in preclinical models for cancer and neurodegeneration, including prion-related disorders and tauopathies [42]. In addition, a new molecule known as integrated stress response inhibitor (ISRIB) limits the consequences of eIF2α phosphorylation by stabilizing the protein translation regulator eukaryotic initiation factor 2B (eIF2B) [48,49]. ISRIB also alleviates neurodegeneration in PrD models with no reported toxicity [50]. Moreover, recent drug discovery efforts identified novel compounds, named dibenzoylmethane and trozodone, approved by the Food and Drug Administration, that mimic the effects of ISRIB [51,52].

IRE1 is a transmembrane kinase and endoribonuclease that undergoes dimerization and autophosphorylation upon ER stress (Fig. 1) [53]. IRE1 catalyzes the nonconventional splicing of the mRNA encoding X-

box binding protein 1 (XBP1) through the excision of a 26 nt intron [54,55], followed by a religation by RctB [56]. This processing event shifts the open reading frame of the mRNA, enabling the expression of its active and stable form known as XBP1 spliced form (XBP1s) [20]. XBP1s controls the transcription of a large cluster of genes involved in lipid biosynthesis, ER and Golgi biogenesis, among other events [57–59]. The nonprocessed XBP1 mRNA (XBP1u) produces an unstable protein that can act as a repressor of its own activity, but also contributes to XBP1 mRNA substrate delivery to the ER [60]. In addition, the endoribonuclease activity of IRE1 can degrade certain subsets of mRNAs or microRNAs through a process called regulated IRE1-dependent decay (RIDD). This alternative output of IRE1 has been associated with the degradation of mRNAs encoding ER cargo proteins, contributing to reduce the load of luminal misfolded proteins [61]. In addition, RIDD can degrade mRNAs involved in the regulation of inflammation, cell migration and metabolism, among other biological processes [61–63]. RIDD has also been associated with the control of cell fate under ER stress, contributing to apoptosis through caspase activation and death receptors modulation [63,64]. Determinants of IRE1 substrate specificity are unclear, but the oligomerization state of IRE1 and stress intensity appear as important factors [60]. IRE1 can also associate itself with tumor necrosis factor receptor-associated factor 2 (TRAF2) and other adapter proteins to initiate proinflammatory and potentially proapoptotic signaling through the nuclear factor-κB (NF-κB) or apoptosis signal-regulating kinase 1 (ASK1) and c-Jun N-terminal kinase (JNK) pathways [65,66].

XBP1s is considered as a prosurvival factor, upregulating genes involved in proteostasis control and secretory cell function. Since XBP1s can also promote malignant cell transformation and cancer [67], several screenings of small molecules have been performed to identify IRE1 RNAse inhibitors, including derivatives of salicylaldehydes, 4μ8C, MKC-3946, and STF-083010 [42]. Other compounds, termed kinases inhibiting RNAse attenuator (KIRAs), allosterically bind to IRE1, modulating its oligomerization state and inhibiting its signaling. Interestingly, KIRAs are effective in reducing cell degeneration in models of obesity, diabetes, and retinal damage [68,69].

Under ER stress, the full length ATF6 precursor is exported to the Golgi where it is processed by the proteases S1P and S2P (Fig. 1) [70]. This cleavage yields a shorter cytosolic and active bZip transcription factor termed ATF6f (p50α), which translocates to the nucleus and drives the expression of different chaperones and ER-associated degradation (ERAD) components [71,72]. ATF6f also binds to the XBP1 promoter enhancing its levels, and can also form heterodimers with XBP1s, instigating specific patterns of gene expression [73]. This feature allows dynamic UPR responses, depending on the presence of both factors and the nature of the targeted site [72,73]. Recently, inhibitors and activators of the ATF6 pathway were discovered but their potential use *in vivo* in disease models is still unknown [74,75]. Overall, the UPR represents a coordinated and global signal transduction pathway that triggers adaptive programs to restore proteostasis and sustain cell function through the control of a variety of inter-related outputs. In addition, the UPR integrates information about the intensity, nature and duration of the stress stimuli toward cell fate decisions that could translate into the activation of cell demise pathways.

ER proteostasis alterations in Alzheimer's disease

In the context of AD, different perturbations in the secretory pathway have been shown to result in ER stress. But contrary to the most obvious expectations, ER stress is not necessarily provoked by direct aggregation of AD-related proteins at the ER (Fig. 2) [24,76]. Exposure of neuronal cells to Aβ oligomers or fibrils results in a drastic alteration of ER calcium homeostasis, leading to abnormal protein folding at the ER [77,78]. For instance, the interaction of Aβ oligomers with neuronal *N*-methyl-D-aspartate receptors (NMDA-Rs) can disrupt cytosolic calcium balance, provoking oxidative stress and ER stress-dependent cell death (Fig. 2) [79]. Tau has been also shown to block the ERAD pathway, resulting in accumulation of misfolded proteins in the ER lumen [80]. Mitochondrial defects and free radical production are also strong contributors to ER stress, inducing the oxidation of ER proteins possibly by altering the activity of the resident chaperones of the protein disulfide isomerase (PDI) family (Fig. 2) [33,81–83]. In some rare familial AD forms, Aβ peptides also accumulate inside the ER, activating the UPR as demonstrated in induced pluripotent stem cell-derived human neuronal cultures [84]. Finally, Aβ oligomers can inhibit the proteasome, leading to ER stress-mediated apoptosis associated with ASK1 and JNK activation [85,86].

Several studies have indicated the occurrence of abnormal levels of ER stress in the human AD brain. Markers of dysfunctional ER proteostasis correlate with the progression of AD and are associated with an activation of UPR sensors and their downstream

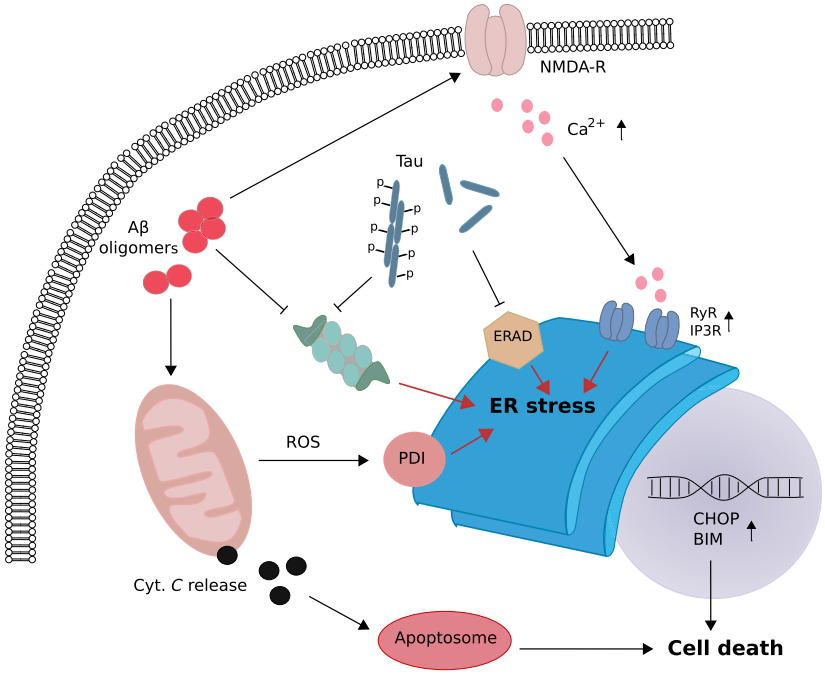

Fig. 2. ER stress in Alzheimer's disease. Molecular mechanisms of AD reveal different perturbations provoking ER stress. Aβ peptide aggregates engage and inhibit NMDA-R, causing an influx of calcium into the cytoplasm. In addition, a change in levels of inositol-1,4,5,-trisphosphate receptor (IP3-R) and ryanodine receptor (RyR) channels can also alter calcium homeostasis and trigger cell death through the mitochondrial apoptosis pathway (apoptosome-dependent). Mitochondrial dysfunctions 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 proapoptotic events controlled by the UPR including the upregulation of BCL-2 like protein 11 and CHOP. Tau soluble proteins interact with and inhibit ERAD activity, triggering accumulation of misfolded proteins in the ER. Hyperphosphorylated tau is also an inhibitor of the proteasome. ROS, reactive oxygen species.

effectors [24,87–89]. PERK is found phosphorylated along with its main target, eIF2α, especially in the hippocampal area where they colocalize with abnormally phosphorylated tau but not tangles [87]. Phosphorylated IRE1 is also detected in AD brain tissues and directly correlates with the Braak stage, increasing its phosphorylated state as the disease progresses [90]. The expression of UPR downstream targets is also altered in AD brain relative to nondemented control subjects. BiP expression is induced in the hippocampal and cortical areas, showing an increased staining in healthier neurons [89,91]. A full set of other chaperones, such as Hsp72, Grp94, PDI and calreticulin, are induced in AD brain tissue and cerebrospinal fluid [83,89,92]. The proapoptotic UPR transcription factor CHOP is also upregulated [88]. XBP1s, on the other hand, appears to follow a more complex kinetic with reports of a moderate increase or no modulation [88,93,94]. Another feature of altered proteostasis in AD is the accumulation of ubiquitinated proteins [95]. Most of the ubiquitin ligases are known to be less active during aging, an effect bolstered in the AD brain, associated with altered expression of ubiquitin-like modifier activating enzyme 1 (UBA1), E2 enzymes, the E3 ubiquitin ligase HRD1 and the ubiquitin–proteasome system regulator ubiquilin (UBQL
N1) [17].

While the UPR appears to be engaged during AD progresion, the static picture of immunostaining is unable to provide information to define its function opening several relevant questions. Does the UPR operate as an adaptive program to restore proteostasis and sustain neuronal function? Does the UPR affect synaptic function and neuronal plasticity? Is the UPR driving the neurodegenerative process? Is ER stress part of the etiology of AD? In the next sections, we address these questions through the analysis of available data in animal models of AD where UPR signaling has been manipulated with various approaches. A complex scenario is emerging where, depending on the UPR signaling branch manipulated, specific and even opposite effects on central AD features may be observed.

PERK: a time-dependent response

Studies analyzing the impact of PERK signaling in AD models have depicted a contrasted and paradoxical role of this pathway in the progression of the disease. PERK activation seems to precede the formation of tangles in AD human brains, but its activation is also instigated by the accumulation of tau aggregates as reported in transgenic mice [87,96,97]. Interestingly, the effects of PERK activation on protein translation inhibition have also been shown to favor BACE1 accumulation [98]. In fact, the 5′-untranslated region of the mRNA of BACE1 contains upstream open reading frames allowing a higher translation rate after eIF2α phosphorylation [98]. Studies in an animal model of AD showed that ablation of PERK reduces BACE1 protein level and Aβ production [99]. Conversely, exposure of cells to the eIF2α phosphatase inhibitor salubrinal augmented BACE1 protein levels [98].

Injection of Aβ oligomers in the hippocampus specifically induces PERK phosphorylation, leading to local expression of ATF4 in the axonal compartment [100]. This event triggers neuronal degeneration *via* CHOP [100]. Moreover, local expression of ATF4 in axons can induce axonal damage through a cell-non-autonomous mechanism that propagates between neurons [100]. However, in other models PERK signaling was suggested to be neuroprotective [101].

Recent studies in animal models of AD suggest that abnormal PERK activation has detrimental effects to neuronal plasticity and cognition. Importantly, control of protein translation through eIF2α phosphorylation is a well-known negative regulator of synaptic plasticity and learning and memory-related process [102,103]. In addition, ATF4 expression has been shown to repress the transcription factor cAMP response element-binding protein (CREB), an essential component that sustains synaptic function [104–106]. Targeted deletion of the eIF2α kinases PERK or general control non-derepressible 2 (GCN2) improves synaptic plasticity and memory function in the APP/PS1 AD mouse model [107]. Similar results were obtained when PERK was targeted in the AD model 5xFAD [99]. Taken together with previous studies in prion disease models [108], these results suggest that the occurrence of chronic ER stress in AD neurons may result in synaptic dysfunction and cognitive impairment through the repression of synaptic protein expression. In the long term, sustained PERK signaling may also translate into neuronal loss through apoptosis (Fig. 3).

IRE1 and XBP1s: divergent roles in AD

The possible functions of IRE1 and XBP1 in brain physiology and their relation in AD remained unknown until very recently. While IRE1 and XBP1s are normally viewed as a linear pathway, new studies started to isolate distinct functions in AD. Ten years ago, a screening to identify the universe of XBP1s target genes revealed a regulatory network including key factors related to AD pathogenesis [58]. Among those putative targets, genes involved in APP metabolism were identified, such as γ-secretase components (presenilin 1 and 2, nicastrin, and the presenilin enhancer 2), APP trafficking mediators (UBQULN1, Fe65) and the tau kinase Cdk5 [58]. More recently, a genome-wide association study identified an XBP1 promoter polymorphism as a risk factor to develop sporadic AD in the Chinese population [109]. Importantly, the same polymorphism was previously shown to provide an increased risk to develop bipolar disorders and schizophrenia in Japan, associated with reduced expression of XBP1 [110]. Functional studies in cell culture models indicated that XBP1s expression affects different steps of APP maturation and catabolism (Fig. 4). For example, ADAM10, the main enzyme catalyzing the APP α-cut that prevents Aβ generation, is under the transcriptional control of XBP1s [94]. On the other hand, the proamyloidogenic enzyme BACE1 is reduced by XBP1s at the post-translational level [111]. XBP1s upregulates the expression of catalytic components of the ERAD machinery, including the E3 ubiquin-ligase HRD1 [112]. In turn, HRD1 can target BACE1 for degradation or directly interact with APP to reduce its protein expression [111,112]. HRD1 is also able to target p-tau for proteasome-mediated degradation [113]. Interestingly, alterations to HRD1 expression may contribute to the etiology of AD since its protein level is decreased in the human AD brain [114,115]. The expression of XBP1s itself appears transient during the disease [93,94]. This is consistent with the idea of an early increase of XBP1s mRNA as a protective mechanism during ER stress, followed by a decrease of its expression if the stress is not resolved [116]. Recently, the enforcement of XBP1s expression in the hippocampus of AD transgenic mice was reported to reduce Aβ load [93]. Experiments in fly models also suggested that XBP1s overexpression in the eye protects cells against Aβ and tau toxicity [117,118].

As mentioned, IRE1 activation is tightly correlated with the degree of AD histopathology [90]. Our group recently uncovered an unexpected role of IRE1 in AD pathogenesis [90]. Genetic ablation of the RNAse domain of IRE1 in the central nervous system resulted

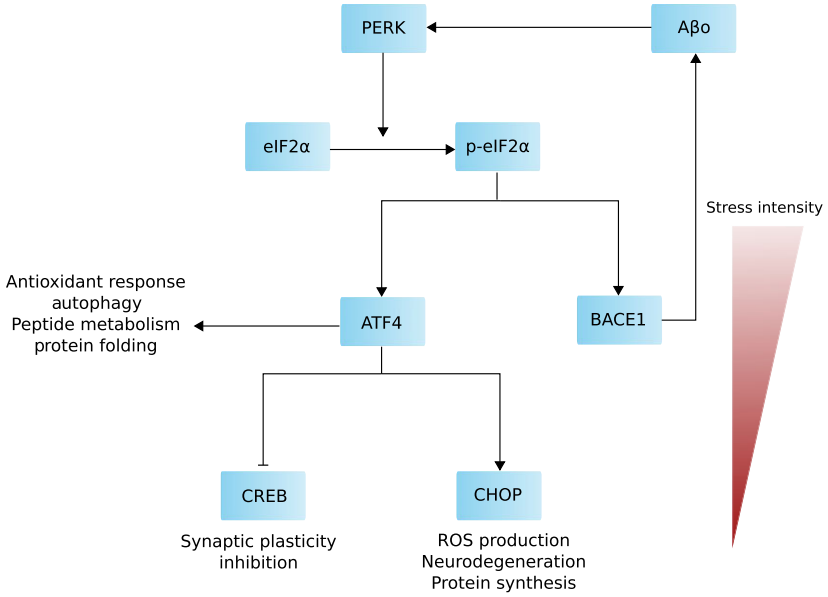

Fig. 3. PERK signaling in AD. PERK activation by ER stress leads to eIF2α phosphorylation and translation inhibition. PERK can induce a cytoprotective response through the induction of many genes related to protein folding, the antioxidant response, amino acid metabolism, and autophagy. Under chronic ER stress, sustained PERK activation results in the upregulation of CHOP *via* ATF4 triggering cell death by apoptosis involving the production of reactive oxygen species (ROS), enhanced protein synthesis, and regulation of the expression of BCL-2 family members. In neurons, ATF4 also act as a repressor of synaptic plasticity, playing a potentially deleterious role during AD. In addition, the control of protein synthesis by PERK can also impact neuronal plasticity and learning- and memory-related processes. ATF4 expression in axons can induce degenerative processes on a cell-nonautonomous manner. Finally, translation inhibition favors BACE1 expression and Aβ oligomers production (Aβo), possibly resulting in more ER stress and initiating a self-sustaining loop.

in a clear decrease of the Aβ load in the brain of AD mice, in addition to reduced neuronal loss and astrogliosis [90]. At the mechanistic level, IRE1/XBP1 signaling was shown to regulate proteosome-mediated degradation of APP (Fig. 4). Interestingly, in other models of neurodegenerative diseases such as amyotrophic lateral sclerosis and Huntington's disease, the genetic suppression of XBP1 expression delayed the progression of the disease in part through the upregulation of autophagy, which eliminated abnormal protein aggregates associated with these pathologies [119,120]. However, no increase of typical autophagy markers was detected after IRE1 deletion in the 5xFAD model [90]. Interestingly, studies in *Caenorhabditis elegans* indicated that targeting XBP1 also protects against Aβ toxicity possibly due to a feedback loop that overactivates IRE1 leading to autophagy induction [121]. This feedback mechanism has been shown to occur in mouse models where XBP1 was deleted in various organs (i.e. liver or pancreas), leading to exacerbated RIDD [122]. Since IRE1 has alternative substrates through RIDD, the function of this specific UPR output in AD remains to be determined.

XBP1s as a core mediator of synaptic plasticity

Studies in peripheral tissues highlighted an essential role of XBP1 in sustaining the function of specialized secretory cells, including B cells, exocrine and endocrine pancreas, and salivary glands among other tissues [122]. In contrast, genetic ablation of XBP1 expression in the brain bypassed embryonic lethality of full knockout mice and did not result in any gross abnormality [123]. Phenotypic screening using a conditional knockout mouse for XBP1 in the nervous system revealed a specific activity of this transcription factor in learning and memory-related processes [124]. Moreover, the ectopic expression of XBP1s in the hippocampus using adeno-associated virus injections or neuronal XBP1s transgenic mice improved the basal performance of animals in learning and memory-related tasks, in addition to enhancing long-term potentiation [124]. These effects were explained by a specific and direct regulation of brain-derived neurotrophic factor (BDNF) by XBP1s [124]. Importantly, BDNF itself is a well-described regulator of neurite outgrow and neuronal plasticity [125,126].

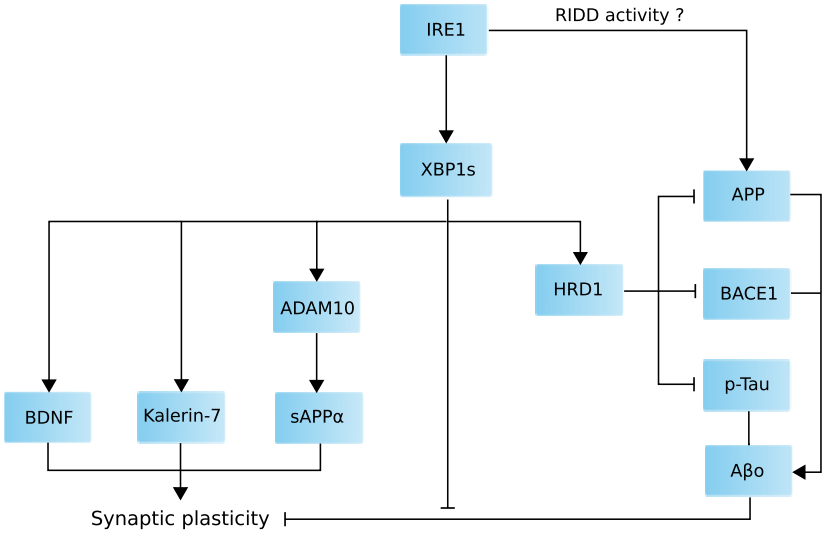

Fig. 4. XBP1s and AD pathogenesis. A full cluster of genes involved directly or indirectly in AD pathogenesis is under XBP1s regulation. Through induction of the E3 ubiquitin ligase HRD1, XBP1s can increase the degradation rate of key AD proteins: APP, BACE1 and p-tau. Direct protection against Aβ or tau toxicity through XBP1s expression has been reported in different models. Interestingly, XBP1s controls a full set of genes involved in synaptic plasticity such as BDNF, Kalerin-7 and the production of the secreted APPα fragment (sAPPα) through ADAM 10 transcription. This highlights XBP1s role in neuronal physiological functions, independently from Aβ or tau toxicity. The neurotrophic factor BDNF can also induce a specific XBP1s splicing by IRE1, without activating the UPR in its entirety. In ER-stress conditions, an IRE1 sustained signal might favor RIDD and proapoptotic activity rather than XBP1s expression. Recent evidence suggests IRE1 as a possible positive regulator of APP expression and Aβ accumulation.

Furthermore, a polymorphism in the human BDNF gene is associated with different psychiatric disorders and memory deficits [127,128]. In addition to controlling BDNF expression, XBP1 also initiates a positive feedback loop in which BDNF increases XBP1 mRNA splicing through the activation of IRE1 [124,129]. A recent report identified the signaling event engaging IRE1 downstream of the BDNF receptor as phosphorylation by protein kinase A, also validating the role of XBP1s in the autoamplifying loop of BDNF to drive its own expression [130]. Another study confirmed the effects of XBP1 on neuronal plasticity and applied these findings to a model of AD. Ectopic overexpression of XBP1s in the hippocampus of AD mice rescued the defects observed in dendritic spine density, long-term potentiation and spatial memory [93]. This phenotype was associated with the control of kalerin-7 expression by XBP1s [93]. Kalerin-7 has been reported to regulate dendritic spine formation through cytoskeleton remodeling [131–133]. Interestingly, levels of kalerin-7 protein are decreased in human AD brain and genetic disruption of kalerin-7 decreases synaptic plasticity and provokes memory impairments in mice [93,131,134]. Overall, these studies place XBP1s as a master regulator of neuronal plasticity, controlling the expression of critical modulators of neuronal physiology (Fig. 4).

Targeting the UPR for therapeutic inervention

Since ER stress is part of the etiology of numerous diseases, such as cancer, diabetes, and PMDs, pharmacological modulation of the UPR is currently under development as possible therapeutic approaches. Considering the increasing evidence showing that the UPR modulates APP metabolism, tau phosphorylation and neuroplasticity, intervention approaches to target the pathway in the context of AD may impact not only ER proteostasis but also other cardinal features of the disease. Overall, only a few drugs targeting the UPR have been tested in preclinical models of AD [42]. The development of a UPR-based pharmacology faces a great challenge because of the essential role of this pathway in many organs, with a high probability of generating side effects in the liver and pancreas among other tissues [135]. Moreover, studies in other PMD models have shown that the contribution of the UPR to the pathology might depend on the disease context, the neuronal population affected and the signaling branch analyzed [24,136,137], making specificity issues a key point to be defined for therapeutic development [41,42].

UPR-targeting drugs can be divided into two major classes: compounds that directly modulate specific UPR components and compounds that indirectly

adjust ER proteostasis by regulating process such as ERAD, protein folding, and degradation [138]. Among direct modulators, compounds that target the PERK branch of the UPR are the most studied drugs in models of neurodegenerative diseases. Most of the available compounds, such as salubrinal, do not target PERK itself, but rather the phosphorylation level of eIF2α through the inhibition of its phosphatase complexes, maintaining the protein translation blockade [139]. As mentioned, the administration of salubrinal to AD models increased the accumulation of Aβ and BACE1 expression [99]. Importantly, other eIF2α inhibitors such as sephin 1 and guanabenz have been tested in various PMD models showing great neuroprotective potential [52]. Other small molecules targeting PERK need to be tested in AD models. Interestingly, oral administration of GSK2606414 alleviated neurodegeneration in tau transgenic mice [140]. However, a recent report suggested that GSK2606414 has a higher affinity for RIP kinases, in addition to generating serious side effects due to pancreatic toxicity [141]. In contrast, the administration of ISRIB provided neuroprotection in a model of prion disease while not triggering any pancreatic toxicity [50]. However, the administration of ISRIB to an AD mouse model did not modify disease pathogenesis [142]. Additionally, ISRIB has poor solubility, which may reduce its translational potential [51]. The recent repurposing of trazodone and dibenzoylmethane as ISRIB mimetics may open other interesting avenues for future testing in AD models since these two compounds had outstanding protective effects after oral treatment of tau transgenic mice [51].

The second most studied UPR pathway to develop new pharmacological molecules is the IRE1–XBP1s axis, especially for the treatment of metabolic diseases and cancer. Inhibition of the IRE1 RNAse activity with MKC-3946 or STF-083010 selectively reduced the growth of myeloma tumors in xenograft models, associated with low toxicity [42,143]. Other compounds that efficiently inhibiting IRE1 still lack a complete pharmacological profile and it is not known if they can cross the blood–brain barrier (reviewed in [41]). Another compound, KIRAs, may allosterically binds and inhibits IRE1, reducing the deleterious effects of its signaling in models of diabetes and obesity [68,69].

Chemical chaperones are small molecules that stabilize proteins and have been shown to reduce ER stress levels. Three main chemical chaperones have been extensively studied and are approved by the Food and Drug Administration, namely 4-phenylbutyric acid, trehalose, and tauroursodeoxycholic acid. Treatment of cells and animals with these small molecules has been shown to be protective against ER stress in various cell types and disease models [144]. For instance, 4-phenylbutyric acid ameliorates cognitive decline in tau transgenic mice [145]. Tauroursodeoxycholic acid administration reduces amyloid deposition in AD mice and improves cognitive capacity [146]. Trehalose has been also shown to protect against AD pathogenesis [147]. While chemical chaperones need further characterization in AD models, they constitute a possible avenue for future therapeutic development.

Gene therapy is emerging as a feasible strategy to specifically target distinct brain regions and may be effective in modulating ER proteostasis [148]. We speculate that a more direct way to reduce ER stress and improve the functionality and survival of affected neurons in AD will be the delivery into the brain of vectors encoding active XBP1s, ATF6, or ER chaperones. As discussed, the injection of XBP1s into the hippocampus using lentivirus has been shown to improve neuronal functions in AD neurons [93]. In addition, the therapeutic potential of the UPR may impact other aspects of the disease that are beyond synaptic protein expression and ER stress buffering. In addiiton to neuronal plasticity, other neuroprotective effects of XBP1s-based gene therapy have been reported, improving peripheral axonal regeneration [149], increasing motor recovery after spinal cord injury [150], reducing the loss of dopaminergic neuron models of PD [151], and reducing protein aggregation of mutant huntingtin [152].

Perspectives

The activation of the UPR in AD was first proposed as a downstream cellular response to Aβ or tau accumulation rather than a key feature of the disease. Nowadays, numerous studies have shifted the way we view the involvement of the UPR in AD, placing the pathway as an important player in disease pathogenesis and possible therapeutic interventions. Available data suggest that ER stress signaling may influence the amyloid cascade, tau phosphorylation, and synaptic dysfunction through distinct mechanisms. Moreover, recent discoveries indicate that UPR imbalance in AD might impact neuronal functions independently from Aβ or tau toxicity. Because the UPR has numerous roles, even beyond the regulation of cellular proteostasis, this pathway might be connected to other relevant features of AD (Fig. 5). For instance, metabolic defects, insulin resistance and lipid homeostasis dysregulation are considered as important components of AD etiology [153–155]. The ER stands as the main organelle involved in lipid metabolism and the UPR has been shown to regulate lipid synthesis, notably through the transcription factor XBP1s, RIDD, and

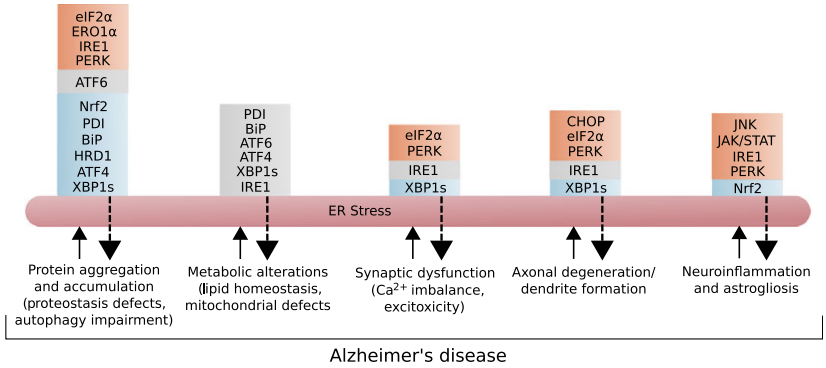

Fig. 5. Contribution of the UPR to Alzheimer's disease lesions. The major molecular features of AD, such as protein aggregation, calcium imbalance, metabolic alterations and brain inflammation, can induce ER stress and be modulated by the UPR. Various factors of the UPR network could be connected to these lesions and are described as protective (blue bars), contributors to the pathogenesis (red bars) or possessing undetermined functions (gray bars). JAK, Janus kinase; STAT, signal transducer and activator of transcription.

ATF4 [156–159]. Alternatively, alteration of membrane lipid composition has been reported to be a possible activator of the UPR [157,160]. Thus, the occurrence of chronic ER stress in AD could directly contribute to altered brain lipid content, insulin resistance and accumulation of neurotoxic concentrations of lipids such as ceramides. In addition, the activity of the UPR is essential for the normal function of immune cells including macrophages, dendritic cells and B cells, modulating inflammatory responses and cytokine production [161]. Overall, there are still many gaps that need to be filled in order to understand the implications and significance of UPR signaling to different aspects of AD.

During the past 5 years, a major development and improvement of strategies for gene therapy has been observed and this could constitute an interesting alternative to pharmacology. In the context of neurodegenerative diseases, gene therapy possesses multiple advantages, including high specificity, local delivery to specific brain areas and no systemic side effects [148,162]. Adeno-associated viruses are the current choice for gene therapy in the central nervous system, showing an outstanding safety profile as reported in many clinical trials [162]. The availability of different viral serotypes would also allow a more selective targeting of selected neuronal populations. Several preclinical studies have shown extensive protective effects of UPR-based gene therapy in various models of PMDs [148]. The recent positive outcome to delivering the XBP1s cDNA into the brain of AD mouse models promises interesting avenues for future therapeutic intervention [93].

Since XBP1s may cooperate with oncogenes to develop malignant brain tumors [67], the possible negative effects of a long-term administration of UPR-based gene therapy for brain diseases need to be seriously addressed. Importantly, our group has kept transgenic mice overexpressing XBP1s in neurons for 2 years without observing any signs of tumorigenicity (unpublished results), suggesting that XBP1s overexpression in the brain may be safe. Further studies are still needed to fully address the potential of the ER proteostasis network as a target for AD. The fact that the UPR influences cardinal features of AD, including abnormal protein aggregation, cellular stress and synaptic function, it places the pathway as a convergent point that integrates different cellular processes involved in AD pathogenesis.

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