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Possible involvement of endoplasmic reticulum stress in the pathogenesis of Alzheimer's disease

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Abstract: The endoplasmic reticulum (ER) is an organelle that plays a crucial role in protein quality control such as protein folding. Evidence to indicate the involvement of ER in maintaining cellular homeostasis is increasing. However, when cells are exposed to stressful conditions, which perturb ER function, unfolded proteins accumulate leading to ER stress. Cells then activate the unfolded protein response (UPR) to cope with this stressful condition. In the present review, we will discuss and summarize recent advances in research on the basic mechanisms of the UPR. We also discuss the possible involvement of ER stress in the pathogenesis of Alzheimer's disease (AD). Potential therapeutic opportunities for diseases targeting ER stress is also described.

Keywords: Alzheimer's disease, pathogenesis, therapeutics development, endoplasmic reticulum stress, unfolded protein response

Abbreviations

a disintegrin and metalloproteinase 10 (ADAM10), Alzheimer's disease (AD), apoptosis signal-regulating kinase 1 (ASK1), activating transcription factor 4 (ATF4), activating transcription factor 6 (ATF6), C/EBP-homologous protein (CHOP), eukaryotic initiation factor 2 (eIF2α), endoplasmic reticulum (ER), ER-associated degradation (ERAD), Huntington's disease (HD), inositol-requiring enzyme-1 (IRE1), integrated stress response inhibitor (ISRIB), c-Jun N-terminal kinase (JNK), double stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK), regulated IRE1-dependent decay (RIDD), TNF receptor-associated factor 2 (TRAF2), unfolded protein response (UPR), X-box binding protein 1 (XBP1)

1 Introduction

The endoplasmic reticulum (ER) is an important organelle involved in the quality control of proteins, particularly protein folding, and maintaining intracellular Ca^{2+} homeostasis. However, when cells are exposed to stressful conditions, which perturb ER function, aberrant unfolded proteins accumulate. Evidence to indicate the exposure of cells to various physiological stress signals that promote ER stress is increasing (Fig. 1). For example, hypoxic stress has been shown to induce the activation of double stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK) and phosphorylation of eukaryotic initiation factor 2 (eIF2α), indicating a cause of ER stress [1]. PERK is activated in brain ischemia and reperfusion [2], and the ER stress-induced apoptotic transcription factor, C/EBP-homologous protein (CHOP)-mediated neuronal cell death has been observed in brain ischemia [3]. Glucose deprivation has also been shown to induce ER stress in various cellular models [4-7]. Hyperhomocysteinemia, a risk factor for cardiovascular disease or Alzheimer's disease, reportedly induces ER stress [8-12]. Homocysteine has been shown to induce ER stress in human umbilical vein endothelial cells [8, 9], and in the livers of cystathionine β-synthase-deficient mice with hyperhomocysteinaemia [9, 10]. Furthermore, an injection of homocystenine into mice increases X-box binding protein 1 (XBP1) splicing in the brain [13]. In addition to these physiological stress signals, it has been well known that abnormal Ca^{2+} concentration by thapsigargin treatment and no sugar addition by tunicamycin treatment induce ER stress. Toxic chemical

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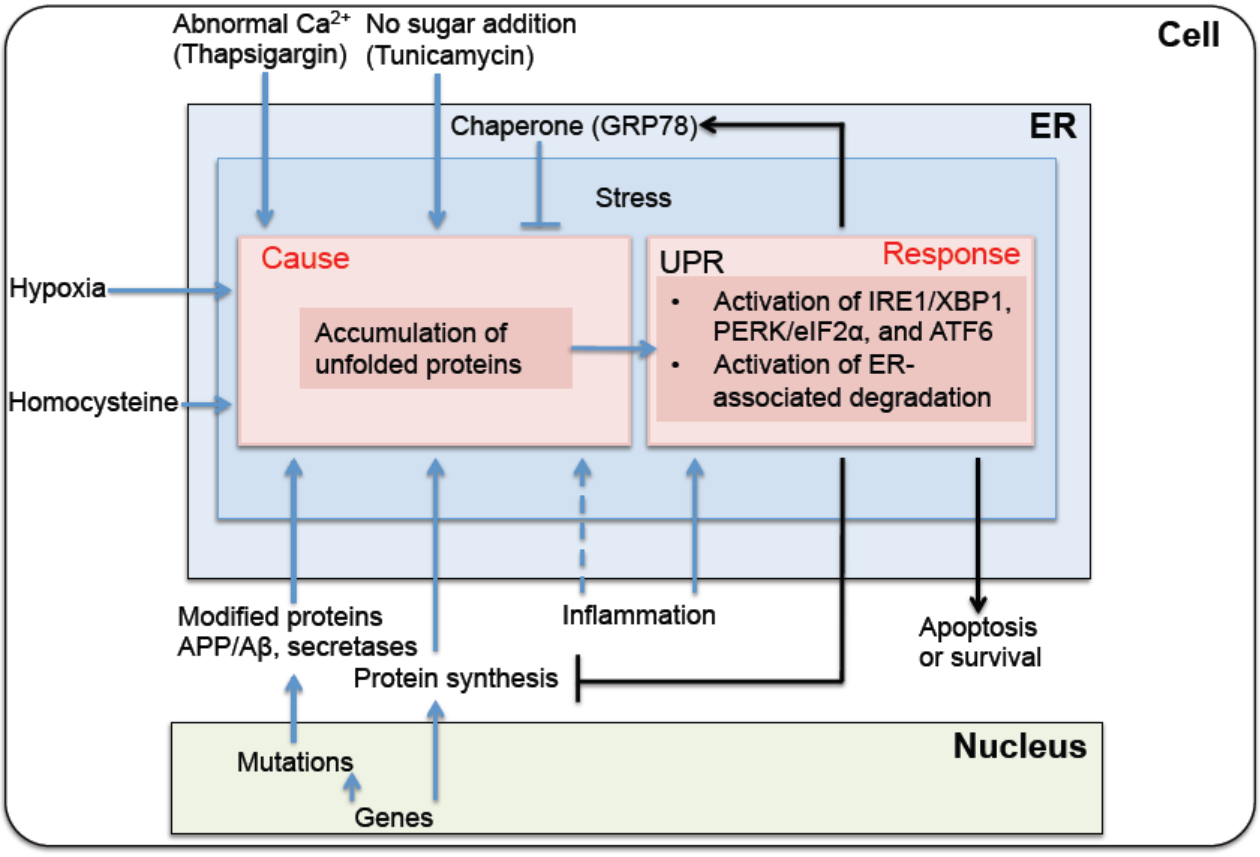

Figure 1: Proposed relationships between ER stress and UPR in AD. Participation of mutation, protein modification, inflammation, APP/Aβ, secretases and chaperons in AD pathogenesis. Abnormal Ca^{2+}, no sugar addition, hypoxia and homocysteine will induce ER stress. APP: Amyloid precursor protein. Straight lines suggest possible involvement. A dotted line suggests presumable involvement.

compounds such as endocrine-disrupting chemicals have also been reported to disrupt ER functions [14-16].

The inhibition of ER function leads to the accumulation of unfolded proteins in the ER (Fig. 1). Accumulation of unfolded proteins is unfavorable to cells. This condition causes stress to the ER. On the other hand, cells resist against such an unfavorable condition by activating several stress sensor proteins in the ER to cope with such a stress. Following activation of stress sensor proteins cells respond: inhibition of biosynthesis of new proteins, degradation of unfolded proteins, and influence on cell survival/apoptosis [17-22]. These responses are termed unfolded protein response (UPR). Under the UPR, three branches are induced by stress sensor proteins such as inositol-requiring enzyme-1 (IRE1), PERK, and activating transcription factor 6 (ATF6), which localize in the ER. These activated UPR components transmit signals to the nucleus and induce genes to address these issues. Upon the accumulation of unfolded proteins in the ER, cells also activate an ER-associated degradation (ERAD) signal, which increases the degradation of unfolded proteins by a ubiquitin-proteasome pathway (Fig. 1). In the following sections, we briefly summarize the basic mechanisms of UPR, and then discuss the link between ER stress and the pathogenesis of Alzheimer's disease (AD).

2 Mechanisms underlying the unfolded protein response

Cells activate three major pathways of UPR, in which IRE1, PERK, and ATF6 are mainly involved, upon the accumulation of unfolded proteins in the ER. Upon accumulation of unfolded proteins, GRP78 dissociates from the luminal domain of IRE1, PERK, and ATF6, which subsequently induces activation of these ER sensor proteins [23-25]. Alternatively, IRE1 would also recognize unfolded protein directly and activate UPR [26, 27]. UPR-related gene expression is controlled through the activation of these UPR components (Fig. 1). We briefly overview the molecular and functional characteristics of each UPR component.

2.1 IRE1α

IRE1α is a type 1 transmembrane Ser/Thr protein kinase protein. Upon activation, IRE1, in turn, activates c-Jun N-terminal kinase (JNK) through TNF receptor-associated factor 2 (TRAF2) [28]. IRE1-mediated JNK activation has been shown to mediate autophagy under ER stress [29]. In addition, apoptosis signal-regulating kinase 1 (ASK1) is involved in ER stress-induced JNK activation, which may be linked to Huntington's disease (HD), spinobulbar muscular atrophy (SBMA), dentatorubral-pallidoluysian atrophy (DRPLA), and six spinocerebellar ataxias [30]. IRE1α also exhibits endoribonuclease activity, which catalyzes the processing of XBP1 mRNA. ER oxidoreductase protein disulfide isomerase A6 (PDIA6) interacts with IRE1 and enhances its activity by increasing its phosphorylation and XBP1 mRNA splicing [31]. Upon activation, the 26-bp intron of XBP1 mRNA is spliced out and flame shifted, spliced XBP1 protein is produced [32]. Spliced XBP1 (sXBP1) functions as a transcription factor that regulates UPR-related genes. In addition to the above functions, Weissman's group have reported that IRE1α degrades certain mRNA encoding proteins secreted during ER stress, which is named regulated IRE1-dependent decay (RIDD) [33].

2.2 PERK

PERK, a type 1 transmembrane kinase protein localizing in the ER, is oligomerized and phosphorylated under ER stress. Active PERK phosphorylates eIF2α. Phosphorylated eIF2α, in turn, has been shown to inhibit the guanine nucleotide exchange factor eIF2B [34], which subsequently inhibits translation. By inhibiting translation, cells cope with stress by reducing the accumulation of unfolded proteins. On the other hand, the phosphorylation of eIF2α is known to be negatively regulated through phosphatases. To date, two types of phosphatases, PPP1R15A (also known as GADD34) and PPP1R15B (also known as CReP), are shown to be involved in the dephosphorylation of eIF2α. PPP1R15A is an inducible protein that is induced through the eIF2α-ATF4 pathway [35-37]. ATF4 is a transcription factor, that is translated through eIF2α [38]. Therefore, PPP1R15A may be a negative feedback regulator of PERK-eIF2α signaling. On the other hand, PPP1R15B is previously reported to be constitutively expressed and inhibited the baseline phosphorylation of eIF2α [39].

2.3 ATF6

ATF6 is a type II transmembrane protein, with a bZIP domain [40]. In its normal state, ATF6 interacts with GRP78 and is retained in the ER. In addition, ATF6 forms complex with calreticulin [41]. When unfolded proteins accumulate in the ER, GRP78 dissociates from ATF6 and ATF6 then moves to the Golgi apparatus and be cleaved by Golgi specific proteases, site 1 protease (S1P) and site 2 protease (S2P) [42]. The N-terminal cleaved product of ATF6 (p50ATF6) then acts as a transcription factor, which induces UPR-related genes [43]. Several ATF6-related homologs have so far been identified such as old astrocyte specifically-induced substance (OASIS) [44], BBF2 human homolog on chromosome 7 (BBF2H7) [45], and cAMP response element-binding protein 3-like 3 (CREBH) [46].

As summarized above, each stress sensor protein has different characteristics. Through regulating these different UPR components, cells will counteract against the stress. We will next discuss how these UPR components and ER stress are involved in the pathogenesis of AD.

3 ER stress and Alzheimer's disease

AD is a chronic neurodegenerative disease that is characterized by decreased levels of cognitive function. One of the pathological features of the brains of AD patients is the extracellular appearance of senile plaques, which mainly consist of the amyloid β (Aβ) peptide. Several UPR stress sensor proteins such as PERK and IRE1α has been shown to be activated in the AD brain [47, 48]. A previous study reports that mouse caspase-12, an ER-specific caspase, is involved in Aβ-induced neuronal cell death [49]. Subsequent analyses suggest that caspase-4 is involved in Aβ-induced cell death in human neuronal cell lines [50].

ER stress has been shown to enhance γ-secretase activity by up-regulating presenilin-1 (PS1) levels [51]. Missense mutations in the human PS1 gene are involved in the development of familial Alzheimer's disease (FAD). FAD-linked PS1 mutations have been suggested to suppress UPR, which may lead to the progression of AD [52]. The inhibition of UPR signaling and subsequent reductions in GRP78 levels by PS1 mutation may increase neuronal vulnerability to ER stress, which may be involved in the pathogenesis of AD [52, 53]. Missense mutations in the amyloid precursor protein (APP) are also involved in the development of AD. An E693Δ mutation of APP, which lacks glutamate-22 of Aβ [54] has been shown to induce ER stress and neuronal cell death [55, 56].

In addition to FAD, ER stress appears to also be involved in the progression of the sporadic type of AD (SAD). An alternative spliced form of PS2 mRNA lacking

exon 5 (PS2V) has been found in 70 % of SAD patients [57]. This PS2V impairs UPR signaling and increases the secretion of Aβ [58]. Therefore, an aberrant splicing variant of PS2 (PS2V) in SAD may be involved in AD progression by impairing UPR signaling.

The excessive production of nitric oxide (NO) seems to cause neuronal cell death through the activation of capsase [59, 60], and the excessive production of NO is involved in AD progression [61]. NO-induced S-nitrosylation of protein-disulphide isomerase (PDI) inhibits its activity, thereby increasing ER stress-induced neuronal cell death [62]. Therefore, the S-nitrosylation of PDI in the AD brain is perhaps involved in the pathogenesis of AD [62].

Overall, these pathological evidences indicate that ER stress could be involved in both types of AD, i.e.: FAD and SAD. In the following section, we will focus and discuss on the role of each UPR components in the pathogenesis of AD.

4 UPR and Alzheimer's disease

APP is cleaved by several proteases. One of the major cleavages is stimulated through β- and γ-secretases, which generates the Aβ peptide. In contrast, α-secretase reduces the formation of the Aβ peptide and produces a soluble form of APP-α (sAPP-α), which has been shown to exhibit neuroprotective properties [63]. Several UPR components play a role in protecting against neuronal cell death in AD.

4.1 Protection of Alzheimer's disease by sXBP1 and ADAM10

A previous study reports that Aβ induces XBP1 splicing and the spliced form of XBP1 (sXBP1) then protects against Aβ-induced neuronal cell death [64]. Furthermore, sXBP1 has been shown to induce a disintegrin and metalloproteinase 10 (ADAM10), which activates the α-secretase involved in APP processing [65]. ADAM10 is previously shown to increase sAPP-α levels [66, 67], which also protects against neuronal death [68-70]. Two rare mutations (Q170H and R181G) in ADAM10 are found to attenuate the α-secretase activity-mediated cleavage of APP, thereby leading to AD-related pathology [71]. Therefore, sXBP1-induced ADAM10 may be involved in neuroprotection in AD [72] (Fig. 2). The polymorphism of -116C/G in the XBP1 promoter has been associated with the risk of AD [73]. Since the transcriptional activity of XBP1 is lower in the -116G allele [74], the neuroprotective effects of XBP1 in AD patients may be lower in this polymorphism.

4.2 Progression of Alzheimer's disease by PERK and eIF2α

Several lines of evidence have indicated that the phosphorylation of PERK and eIF2α is increased in the AD brain [75-77]. The phosphorylation of eIF2α has been shown to increase β-site APP cleaving enzyme-1 (BACE1) levels, thereby enhancing the production of Aβ in neurons [78]. Thus, the chronic induction of eIF2α phosphorylation in the AD brain appears to cause an increase in Aβ production, followed by neurodegeneration (Fig. 2). The suppression of PERK is found to alleviate synaptic plasticity and memory dysfunctions in AD [79]. A previous study demonstrates that reductions in eIF2α phosphorylation enhances the late phase of long-term potentiation and memory in mice [80]. Therefore, dementia in AD may be mediated via the enhanced phosphorylation of eIF2α.

4.3 HRD1 (ubiquitin ligase E3), GRP78, and tau protein in Alzheimer's disease

The activation of ERAD also appears to be involved in the pathogenesis of AD. The ubiquitin ligase E3 has been demonstrated to ubiquitinate unfolded proteins and lead to the degradation of the proteins by 26S proteasome. HRD1, an ubiquitine lygase 3, is shown to bind to and ubiquitinate APP [81] (Fig. 2), followed by the degradation of APP by the proteasome system [82], thereby reducing the production of Aβ [81]. HRD1 protein levels are found to be reduced in postmortem preparations of the cerebral cortex from AD patients, possibly through insolubilization due to oxidative stress [81, 83].

Expression levels of GRP78 has been found to be decreased in the brains of AD patients [52]. GRP78 has been shown to act as a chaperone, which interact with unfolded proteins and recovers folding of the proteins. GRP78 is also known to interact with APP and inhibit its maturation [84, 85] (Fig. 2). Furthermore, the overexpression of GRP78 inhibits soluble APP and Aβ production [84, 85]. These findings suggest that GRP78 directly or indirectly affects the activity of β/γ-secretases by binding to APP. Therefore, GRP78 is involved in pathogenesis of AD by regulating APP processing and Aβ production. However, the precise molecular mechanisms of GRP78 in APP processing have not yet been elucidated.

On the other hand, the accumulation of tau protein (Tau) has been reported to impair ERAD activity, which may be involved in the progression of AD [86]. Therefore, Tau accumulation may impair the protein quality control system of ER in AD. The involvement of α-synuclein (α-SN) in ERAD functions as well as in the pathogenesis of AD has

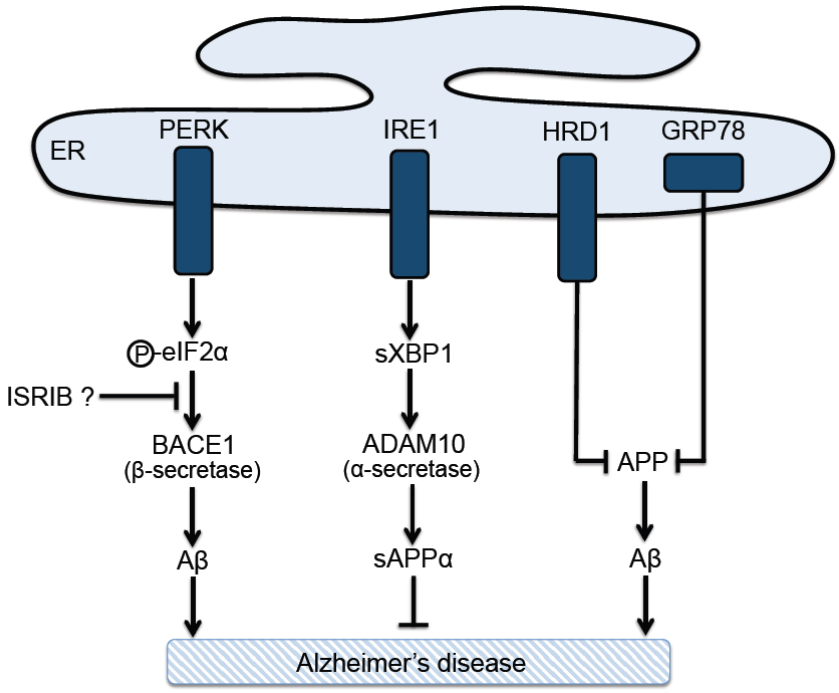

Figure 2: Possible involvement of UPR in the progression and suppression of AD. The phosphorylation of eIF2α increases BACE1 levels, which activates β-secretase activity and induces the production of Aβ. On the other hand, the induction of sXBP1 induces ADAM10, which activates α-secretase activity. ADAM10 induces the soluble form of APP-α, which may protect against neuronal cell death, thereby inhibiting AD progression. The recently identified compound, ISRIB, may be a candidate compound for the treatment of AD. We currently do not know whether ISRIB is useful as a treatment for AD, therefore, future experiments are needed. HRD1 and GRP78 results in the reduction of Aβ by interaction with APP.

not yet been clarified. The pathological roles of Tau and α-SN in relations to the ER stress response in AD remain to be clarified in the near future.

These observations suggest IRE1-XBP1 signal may be a protective response against AD through up-regulating ADAM10. On the other hand, PERK-eIF2α signal may worsen AD through up-regulating BACE1 (Fig. 2). HRD1 seems to inhibit AD progression through decreasing Aβ production. It is interesting that different UPR components play different role in AD. Future analysis may be required to elucidate the role of these UPR components on AD pathogenesis.

5 ER stress, immune functions, and neuro-glial interactions in the progression of Alzheimer's disease

Evidence to indicate that immune reactions are linked with the induction of UPR is increasing [87]. XBP1 is previously reported to induce the production of interleukin (IL)-6 in B cells [88]. Lipopolysaccharide (LPS), a Gram-negative bacterial cell wall component, has been shown to induce XBP1 splicing in macrophages through Toll-like receptors (TLR), sensors of pathogens [89]. Furthermore, IRE1α is shown to promote the production of IL-4 by stabilizing its mRNA in T cells [90]. Inflammation has been reported to induce UPR/ER stress. For instance, tumor necrosis factor α (TNFα) induces UPR in murine fibrosarcoma L929 cells [91]. Interferon-γ (IFN-γ)-induced apoptosis is associated with ER stress in oligodendrocytes [92]. The pathogenesis of AD appears to be associated with inflammation [93]. Glial cells such as microglia is activated by inflammation, which subsequently increases phagocytosis [94, 95]. Activated microglia may increase Aβ clearance through phagocytosis and protect against AD [96, 97]. On the other hand, inflammation results in nitric oxide (NO) production from glial cells [98]. Excessive production of NO will cause neuronal cell death [61]. Therefore, inflammation may be involved in progression as well as prevention of AD. The crosstalk between ER stress and immune functions appears to be involved in the progression of AD [99] (Fig. 3). In brain tissue, glial cells, such as microglias and astrocytes, induce inflammatory cytokine production. Indeed, prostaglandin (PG) E_2 plus interferon (IFN) γ-induced IL-6 production

is synergistically enhanced under ER stress in glial cells [100]. These glial inflammatory reactions affect neuronal functions. Such neuron-glial communication is presumably involved in the progression of AD.

The utilization of glucose is shown to be decreased in the AD brain [101, 102]. Glucose deprivation induces ER stress in neurons and glial cells. It is reported that glucose deprivation increases eIF2α phosphorylation and induced BACE1 expression in neurons [78]. The activation of BACE1 results in Aβ production. Therefore, glucose deprivation may increase the production of Aβ in neurons in the AD brain [78]. As well as neuronal cells, glucose deprivation has been shown to affect glial functions. Glucose deprivation reportedly induces ER stress and the production of IL-6 in glial cells [6]. Furthermore, the neuroprotective effects of PGE_2 plus IFNγ-activated glial cells have been observed under glucose-deprived conditions [6]. These findings suggest that glial cells protect against neuronal cell death under ER-stressed conditions. Thus, the link between ER stress and immune functions in glial-neuronal communication plays an important role in the progression and/or prevention of AD (Fig. 3).

Immune activated glial cells seem to affect neuronal function. Immune function may be associated with ER stress. Therefore, neuro-glial interactions play a key role in the progression of AD. Based on these observations, it is an important future subject to elucidate molecular mechanisms of AD pathogenesis.

6 Possible therapeutics for Alzheimer's disease targeting ER stress

Since several UPR components are involved in the progression of AD, pharmacological modulators of UPR will be useful as a treatment.

6.1 Inhibitors of the integrated stress response (ISR)

Since the suppression of PERK alleviates synaptic plasticity and memory dysfunctions in AD [79], eIF2α signaling may be a significant target of AD therapeutics. The natural product arctigenin has been reported to ameliorate AD by inhibiting eIF2α signaling, BACE1 expression, and Aβ production in neuronal cells [103]. Phosphorylated eIF2 at serine-51 is previously shown to inhibit nucleotide exchange by eIF2B. A chemical inhibitor of the integrated stress response (ISRIB), which inhibits integrated stress responses by activating the eIF2B δ subunit of guanine nucleotide exchange factor (GEF) [104, 105], is recently found to enhance memory in rodents [106]. Furthermore, ISRIB has been shown to attenuate neurodegeneration in prion-infected mice [107]. On the other hand, the attenuation of eIF2α phosphorylation in beta cells causes a severe diabetic phenotype in mice [108]. Thus, ISRIB

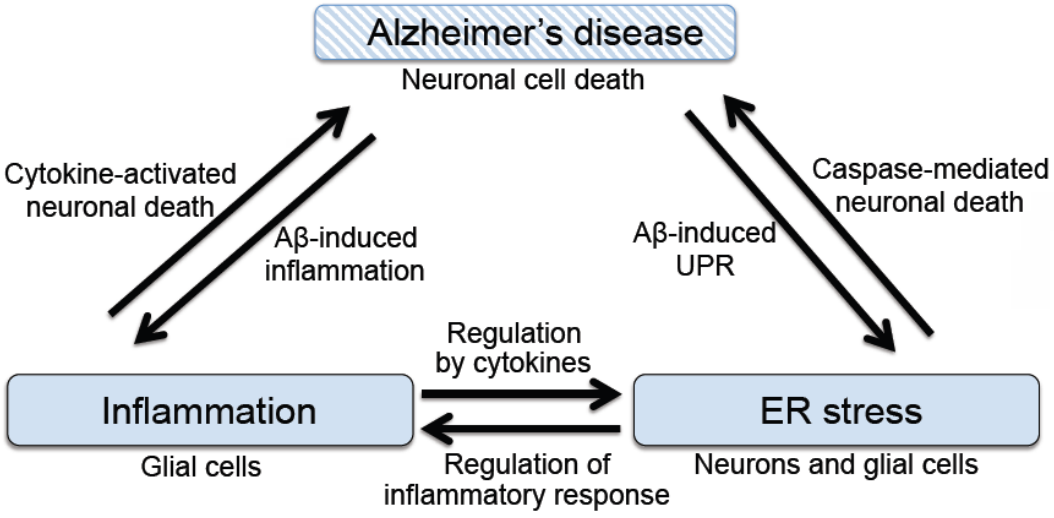

Figure 3: Possible underlying mechanisms involved in the progression of AD. There may be a bidirectional relation between inflammation and ER stress in AD. ER stress regulates immune functions and activates UPR. Cytokines are mainly produced through glial cells. This inflammation may be involved in the progression of AD. On the other hand, accumulation of aggregated Aβ in AD brain increases glial inflammation as well as ER stress-mediated neuronal cell death. Inflammatory cytokines may regulate UPR (ER stress) in glial cells. ER stress affects glial inflammatory responses and caspase-mediated neuronal cell death. These effects may be involved in progression of AD.

may cause pancreatic dysfunctions. However, ISRIB does not cause marked pancreatic dysfunctions in mice [107]. Therefore, ISRIB is presumably useful as an AD treatment without these side effects (Fig. 2). However, we do not currently know whether ISRIB is useful for the treatment of AD, which will be an interesting future subject. Overall, these findings suggest that the modulation of UPR is an attractive strategy for treatments.

6.2 Chemical chaperones

Another strategy for treating AD will be the usage of chemical chaperones, compounds that stabilizes proteins and ameliorate the accumulation of unfolded proteins. Several compounds have been reported to exhibit chaperone activity, which can attenuate ER stress [109-113]. 4-phenylbutyrate (4-PBA) has chemical chaperone activity, and a treatment with 4-PBA is shown to ameliorate cognitive deficits of AD in mice [114]. Furthermore, 4-PBA reverses the reductions observed in GRP78 in the AD model mouse brain [72]. The effects of 4-PBA appears to be, in part, mediated through chemical chaperone activity [115]. Mimori and others report [116-118] that 4-(4-methoxyphenyl) butanoic acid, a synthetic derivative of 4-PBA, possesses more highly inhibitory activity than 4-PBA against protein aggregation and ER stress-induced neuronal death. Tauroursodeoxycholic acid (TUDCA) also has chaperon activity [119, 120], which was shown to attenuate Aβ-induced cell death [121]. However, the clinical effects of chemical chaperones against AD are currently unknown, therefore, future analyses are required.

In relationship to the role of ubiquitin ligase E3 in ERAD, HRD1 will be a possible target for development of AD therapeutics. Since HRD1 is insolubilized by probable oxidation [81, 83], antioxidant compounds seem to be the candidates.

6.3 Anti-inflammatory drugs

The chronic inflammatory condition associated with the progression of AD and clinical application of anti-inflammatory drugs to AD have been considered. Epidemiological studies suggest that several nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful for reducing the progression of AD [122]. Several NSAIDs have been reported to regulate UPR [112, 123, 124]. Thus, several NSAIDs are candidates that are able to regulate UPR as well as inflammation, which may be effective as an AD therapy.

As mentioned in the present section, there would be several strategies for treating AD. Currently we do not know which strategy will be most efficient way to treat AD. On the other hand, combined strategies of several methods mentioned above would also be possible. Moreover, the usefulness of each strategy would be dependent on the stages of AD. Future analyses are required to elucidate whether targeting UPR/ER stress would be useful for the treatment.

7 Concluding remarks

We herein reviewed the possible involvement of ER stress in the progression of AD. Accumulating evidence suggests ER stress is also involved in the pathogenesis of not only neurodegenerative diseases, but diabetes, obesity, and cancer [125-131]. Therefore, elucidating the detailed mechanisms of ER stress will undoubtedly be important for understanding various types of diseases. Furthermore, manipulating the UPR and/or inhibiting unfolded protein accumulation will be a useful strategy for treating these diseases. Meanwhile, since the UPR is also involved in normal physiological functions [132], it is important to take these possibilities into account when developing therapeutics. The development of novel and original medicines against AD as well as other ER stress-related diseases is needed. We consider the ER stress to be one of the significant targets for developing epoch-making therapeutics against AD and other diseases in the future.

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