Dissecting Endoplasmic Reticulum Unfolded Protein Response (UPR<sub>ER</sub>) in Managing Clandestine Modus Operandi of Alzheimer’s Disease

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Alzheimer’s disease (AD), a neurodegenerative disorder, is most common cause of dementia witnessed among aged people. The pathophysiology of AD develops as a consequence of neurofibrillary tangle formation which consists of hyperphosphorylated microtubule associated tau protein and senile plaques of amyloid-β (Aβ) peptide in specific brain regions that result in synaptic loss and neuronal death. The feeble buffering capacity of endoplasmic reticulum (ER) proteostasis in AD is evident through alteration in unfolded protein response (UPR), where UPR markers express invariably in AD patient’s brain samples. Aging weakens UPR<sup>ER</sup> causing neuropathology and memory loss in AD. This review highlights molecular signatures of UPR<sup>ER</sup> and its key molecular alliance that are affected in aging leading to the development of intriguing neuropathologies in AD. We present a summary of recent studies reporting usage of small molecules as inhibitors or activators of UPR<sup>ER</sup> sensors/effectors in AD that showcase avenues for therapeutic interventions.

Keywords: Alzheimer disease, neurodegenerative diseases, endoplasmic reticulum stress (ER), aging, UPR (unfolded protein response)

INTRODUCTION

Alzheimer’s disease (AD), the most common form of dementia faced by more than 40 million people worldwide, significantly affect morbidity and mortality in aged people (Alzheimer’s Association, 2016; Fiest et al., 2016; Scheltens et al., 2016; Cass, 2017). The most vulnerable group falling as target is above 65 years, which puts aging as the crucial risk factor associated with development of the disease (Alzheimer’s Association, 2016; Fiest et al., 2016; Scheltens et al., 2016; Cass, 2017). AD is a progressively neurodegenerative disorder, characterized by cognitive alterations and behavioral changes that owe to synaptic impairment and loss of neurons (Alzheimer’s Association, 2016; Scheltens et al., 2016). Mutations in genes encoding APP (amyloid precursor protein), presenilin 1 and 2 (PS1 and PS2 respectively), as well as ε4 allele of Apolipoprotein E are reported to be linked to rare familial and early development of AD (Selkoe, 2001a,b; Scheltens et al., 2016). AD leads to the formation of neurofibrillary tangles having hyperphosphorylated microtubule associated tau protein and senile plaques of amyloid-β (Aβ) peptide in specific brain regions, result in brain inflammation, astrogliosis and microglial proliferation (Citron, 2002; Selkoe, 2004a,b; Cleary et al., 2005; Haass and Selkoe, 2007; Atwood and Bowen, 2015; Minter et al., 2016; Sami et al., 2017). Gradual
accumulation of Aβ peptide attributed to β- and γ-secretases action on the APP, results in synaptic loss and neuronal death (Chyung et al., 2005; Tatarnikova et al., 2015).

The expression pattern of neurodegenerative pathologies shows distinct molecular signatures, such as misfolded Aβ aggregation and tau protein hyperphosphorylation in the brain (Jiang et al., 2010; Atwood and Bowen, 2015; Sami et al., 2017). How this load of protein aggregates disrupt the neuronal function is still a mystery to medical science? In this review, we have tried to focus on the role of ER stress and the ensuing unfolded protein response (UPRER) imposed on the neuronal cell due to misfolded protein aggregates. Also, we have discussed various therapeutic interventions targeting the molecules involved in UPR pathways aiming at averting the neuropathologies of AD.

**ER STRESS AND UPRER**

Adversities in the endoplasmic reticulum (ER) microenvironment like nutrient deprivation, changes in redox potential, calcium homeostasis, hypoxia and accumulation of unfolded/misfolded protein triggers the UPRER (Schröder and Kaufman, 2005; Moneim, 2015). UPRER is a highly conserved signaling cascade in all eukaryotes involved in the cellular homeostasis (Ellgaard and Helenius, 2003; Mori, 2009; Walter and Ron, 2011) through transcriptional remodeling of ER proteostasis pathways (Lee et al., 2003; Yamamoto et al., 2007; Shoulders et al., 2013; Genereux et al., 2015). The ER lumen harbors various molecular chaperones like the Glucose Regulated Protein 78 kDa (GRP78) that are recruited to misfolded nascent peptides for aiding in their proper folding (Bertolotti et al., 2000; Shen et al., 2002). A plethora of studies have reported UPRER upregulation in the brain samples of Alzheimer’s patients (Hamos et al., 1991; Hoozemans et al., 2005, 2009).

The UPRER embodies a complex network comprised of three stress-responsive transmembrane proteins, Protein Kinase RNA like ER kinase (PERK), Inositol Requiring Element 1 (IRE1) and Activating Transcription Factor 6 (ATF6; Figure 1; Schroder and Kaufman, 2005; Walter and Ron, 2011; Minakshi et al., 2017; Rahman et al., 2017). PERK, a type 1 transmembrane kinase protein, gets trans-autophosphorylated and homodimerized after activation, thereby promoting phosphorylation of serine residues on cytoplasmic eIF2α (eukaryotic initiation factor 2 alpha; Harding et al., 1999; Bertolotti et al., 2000; Ma et al., 2002; Marciniak et al., 2006). Despite the general translational halt induced by the phosphorylated eIF2α (eIF2α-P), certain specific mRNAs bearing internal ribosome entry site (IRES), like the Activating Transcription Factor 4 (ATF4) mRNAs continues to be translated (Harding et al., 2000a; Baumeister et al., 2005). ATF4 regulates genes for various foldases, chaperones, regulatory proteins of the redox and autophagy, cholesterol metabolism etc. (Harding et al., 2003; Fusakio et al., 2016). CCAAT enhancer-binding (C/EBP) protein homologous protein (CHOP) is also a direct target of ATF4 and represents the pro-apoptotic component of the UPRER (Han et al., 2013). In a study, wild type mice subjected to tunicamycin injection showed higher degrees of apoptosis in their renal epithelium as compared to CHOP knockout mice (Marciniak et al., 2004; Onuki et al., 2004). PERK also induces the activation of another transcription factor nuclear factor (erythroid derived 2)-like 2 (Nrf2) independent of eIF2α, which regulates the antioxidant response (Cullinan et al., 2003; Cullinan and Diehl, 2004).

IRE1 is the most evolutionarily conserved ER stress transducer (Tirasophon et al., 1998), which upon activation, undergoes dimerization and trans-autophosphorylation, leading to the activation of its cytosolic endoribonuclease activity that splices a 26-nucleotide intron from the mRNA encoding transcription factor X box binding protein 1 (XBP1) forming XBP1(S) (Yoshida et al., 2001, 2003). The XBP1(S) upregulates genes involved in ER protein maturation and ER-associated degradation (ERAD; Lee et al., 2003; Acosta-Alvear et al., 2007). Cells lacking XBP1 are more sensitive to hypoxia-induced apoptosis (Romero-Ramirez et al., 2004). Upon activation, IRE1 also activates c-Jun N-terminal kinase (JNK) through tumor necrosis factor receptor-associated factor 2 (TRAF2); Zeng et al., 2015). IRE1-mediated JNK activation has been demonstrated to trigger autophagy under ER-stress (Urano et al., 2000).

ATF6 is a type II transmembrane protein, with a basic leucine zipper (bZIP) domain (Yoshida et al., 1998). During the imposed stress, luminal domain of ATF6 loses its association with GRP78, triggering the translocation of ATF6 into the Golgi apparatus where two intramembrane Golgi specific proteases, site 1 protease (SIP) and site 2 protease (S2P), process it. The N-terminal cleaved product p50ATF6 of full length ATF6 (p90ATF), then acts as a transcription factor, which upregulates several genes, including GRP78, Protein Disulfide Isomerase (PDI), XBP1 and CHOP (Haze et al., 1999; Walter and Ron, 2011).

**UPRER IN ALZHEIMER’S DISEASE**

In neuronal pathophysiology, the activation of UPRER can have paradoxical affects. During stress condition, activation of UPRER could reactivate proteostasis; thereby rescuing the neurons by escalating the rate of protein folding through molecular chaperones, or may trigger neurodegeneration and neuronal collapse through the expression of apoptotic markers.

Evidences support the presence of abundant hyperphosphorylated tau protein and ER stress markers in the neurons of the cortex in postmortem brain samples of AD patients (Schepker and Hoozemans, 2015). It is presumed that ER stress is a cell death mechanism triggered by Aβ, and is linked to changes in ER calcium homeostasis (Cornejo and Hetz, 2013). Under the influence of Aβ imposed ER stress, Ca²⁺ leaching from ER is taken up by mitochondria leading to activation of apoptotic death of neurons (Fonseca et al., 2013). The presenilins are responsible for passive ER Ca²⁺ outflow. Documents support that aging neurons fail to maintain tight Ca²⁺ homeostasis across plasma membrane and ER
(Supernet and Bezprozvanny, 2010). Such effects paved the way for “calcium hypothesis of brain aging and AD” (Khachaturian, 1989). Rise in prolonged imbalanced Ca\(^{2+}\) invites ROS accumulation and mitochondrial dysfunction resulting in neuronal death (Supernet and Bezprozvanny, 2010). ER stress may display binary role in AD, firstly modulating the production kinetics of amyloid plaques and secondly altering the cognitive functions in a distinct way (Halliday and Mallucci, 2015). Neurons of AD patients were also characterized by GRP78 induction in temporal cortex and hippocampus and phosphorylation of PERK (p-PERK; Hoozemans et al., 2005).

Active protein synthesis is a hallmark feature of synaptic plasticity and consolidation of memory (Costa-Mattioli et al., 2009). PERK signaling and protein translation control was linked to the cognitive impairment observed in AD models (Devi and Ohno, 2013, 2014). Impairment of cognitive functions due to the reduction in synaptic protein synthesis is displayed during increased phosphorylation of eIF2\(\alpha\) (Costa-Mattioli et al., 2005, 2009; Jiang et al., 2010). Mitigating the expression of PERK improves cognitive function and synaptic plasticity in an AD model (Devi and Ohno, 2014). Moreover, targeting other eIF2\(\alpha\) kinases like General Control Nonderepressible-2 (GCN2) and dsRNA-dependent protein kinase R (PKR) was also witnessed not only to improve learning and memory processes (Devi and Ohno, 2013), but also reduced inflammation (Lourenco et al., 2013). These results significantly indicate that genetic manipulation of PERK improved cognitive ability of cells to survive under stress conditions induced by A\(\beta\) deposition.

The activation of UPR\(^{ER}\) in early stages of AD could be protective through activation of autophagy. However, sustained UPR\(^{ER}\) activation may be detrimental to the neurons (Hoozemans et al., 2005; Nijholt et al., 2011). The expression of XBP1 in Drosophila where the AD-associated A\(\beta\) peptide was expressed in neurons, led to reduced neurotoxicity, supporting the cytoprotective role of XBP1 (Casas-Tinto et al., 2011). In Caenorhabditis elegans (C. elegans) models expressing aggregation-prone mutant tau variants, XB1 was identified to be playing a similar protective role (Kraemer et al., 2006; Loewen and Feany, 2010). However, reports also suggest that IRE1 interacts with PS1 leading to activation of proapoptotic signaling by JNK (Shoji et al., 2000). The JNK3 (member of JNK family) localized in brain, is highly expressed in brain tissue and cerebrosplinal fluid sample from AD patients (Gourmaud et al., 2015) and the activation of JNK3 exacerbates stress perpetuating AD pathology (Yoon and Jo, 2012).

**AGING, UPR\(^{ER}\) AND ALZHEIMER’S DISEASE**

Aging is the single most important risk factor for AD. Decline in the UPR\(^{ER}\) with advancing age marked by the oxidative damage of ER chaperones, leads to disempowering of protein folding capacity (Rabek et al., 2003; Nuss et al., 2008). Studies report that the levels of GRP78 were low in murine cortex, in rat hippocampus, cortex, cerebellum, as well as in a multitude of organs (Paz Gavilan et al., 2006; Hussain and Ramaiah, 2007; Naidoo et al., 2008). Transcription of PERK mRNA were lowered in the aging rat hippocampus, while an increment was reported in the expression of growth arrest and DNA damage protein 34 (GADD34), because it escapes the effect of eIF2\(\alpha\)-P translational inhibition (Paz Gavilan et al., 2006). Studies on C. elegans revealed that the activation of IRE1 branch of the UPR\(^{ER}\) diminishes during the fertile period of adulthood, manifesting in lowered immunity against ER stress (Taylor and Dillin, 2013). The implication of IRE1/XBP1 tier in aging was proven in C. elegans where IRE1 defect reduced life span (Chen et al., 2009).

**MITOCHONDRIA, OXIDATIVE STRESS AND ALZHEIMER’S DISEASE**

Under the imposed stress, apart from UPR\(^{ER}\) coming to the rescue, the herald of mitochondrial UPR (UPR\(^{mt}\)) ensuing after accumulation of unfolded peptide load is well documented. The pathway focuses on invigorating folding and degradation of misfolded peptides in mitochondrial matrix through the execution of retrograde transcriptional activation (Arnould et al., 2015). AD being a multifactorial malady, the accumulation of A\(\beta\) not only affects ER but also mitochondria. There are accumulating evidences, which support deposition of A\(\beta\) in mitochondrial matrix disrupting signaling of the organelle thereby leading to neurodegeneration (Kawamata and Manfredi, 2017). Impairment in the production and functionalities of metabolic enzymes preferentially of TCA cycle disturbs energy metabolism of the brain. Mitochondrial dysfunction causes depletion of cellular ATP pool and enhanced ROS production, which is well implicated in the pathogenesis of AD (Swerdlow et al., 2014; Hoekstra et al., 2016). Besides, impairment of mitochondrial turnover and function in brain, aging potentiates oxidative stress, leading to significant decrease in the cytochrome C oxidase activity that is associated with rise in oxygen radicals in different regions of postmortem AD brain (Figure 2; Hirai et al., 2001; Mosconi et al., 2007; Krishnan et al., 2012). A strong correlation of the cognitive decline with increase in oxidative stress is observed in AD patients (Revel et al., 2015). Incidence of aberrant A\(\beta\) processing ensues after the oxidation of mitochondrial DNA (mtDNA) under stressful circumstances (Volgyi et al., 2015).

Aberrations in mtDNA have been well studied in AD. In an elegant study by Aliev et al. (2013) mtDNA-proliferation and deletion has been reported in AD tissues. Furthermore, the report also illustrates abnormal mitochondrial function in damaged hippocampal neurons in human AD as well as transgenic AD models. In another study using in situ hybridization, Aliev et al. (2008) detected a 5 kB deletion in mtDNA under oxidative stress in abnormal neurons. Such mitochondrial anomalies were also reported to help in AD pathogenesis in A\(\beta\) transgenic mice (Aliev et al., 2008).
FIGURE 1 | Targeting unfolded protein response (UPR) to manage Alzheimer’s disease (AD) with specific molecules. PERK/eIF2α: the phosphorylation of eIF2α shuts down global translation in the cell but for gene-specific translation upregulation of mRNA with internal ribosome entry site (IRES), for example β-site APP cleaving enzyme-1 (BACE1), the β-secretase enzyme (Ohno, 2014). Arctigenin, targets eIF2α-P thereby downregulating BACE1, consequently protects neurons from amyloid-β (Aβ) toxicity. ISRIB, affects eIF2B leading to inhibition of eIF2α-P, which comprehensively restores protein translation and hence enhances long term memory. PERK can be directly inhibited by GSK2606414, leading to halt in tau phosphorylation. Ca2+ leakage induced activation of glycogen synthase kinase-3β (GSK-3β) can be checked by GSK-3β inhibitor I, which prevents Aβ induced phosphorylation of tau. IRE1/XBP1: Quercetin, activates endoribonuclease activity of IRE1 inhibiting tau hyperphosphorylation. The c-Jun N-terminal kinase (JNK) inhibitor, SP600125, inhibits Ca2+ leakage and inhibits Aβ-induced c-Jun phosphorylation.

In a study proving the existence of interlink between mitochondrial dysfunction and AD, the pharmacological/genetic targeting of mitochondrial translation process not only increased life span of GMC101 (model of Aβ proteotoxicity), but also showed reduction in beta-amyloid aggregation in worms and transgenic mouse models of AD (Sorrentino et al., 2017). Treatment of the mitochondrial division inhibitor-1 (mdiv-1) that inhibits mitochondrial fragmentation, thereby rescuing mitochondrial distribution, improves mitochondrial function in CRND8 (AD mouse model) neurons (Reddy et al., 2017; Wang et al., 2017). Treatment with mdiv-1 also causes a decrease in extracellular amyloid deposition and Aβ1–42/Aβ1–40 ratio (Wang et al., 2017). Additionally, SIRT-3, a sirtuin localized to inner mitochondrial membrane, has been found associated with enhancement in the levels of glutathione (Onyango et al., 2002; Someya et al., 2010). As downregulation of SIRT-3 was found to be having a retrograde effect on p53 mediated mitochondrial and neuronal damage in AD, its modulation by therapeutics was found to ameliorate mitochondrial pathology and neurodegeneration in AD (Lee et al., 2018).

DERANGEMENT OF GLUCOSE METABOLISM IN ALZHEIMER’S DISEASE: THE FALLIBLE UPRER

Among the many observed hallmarks of AD, positron emission tomography (PET) revealed a deranged glucose metabolism in brain regions. Aging registers diminished brain glucose utilization that surges in AD (Ivančević et al., 2000). Various reports suggest that UPRER is linked to abnormal glucose metabolism and insulin resistance (Hetz et al., 2015). Type 2 diabetes mellitus (T2DM) has been mechanistically linked to AD pathogenesis, where higher insulin resistance poses a greater risk of AD with reduced glucose uptake in the brain.
Mitochondrial dysfunction in AD: various stress insults like aging and oxidative stress disrupt client protein folding in mitochondria thereby invoking mitochondrial UPR\textsuperscript{mt} (UPR\textsuperscript{mt}). Numerous events line up; there is mitochondrial DNA (mtDNA) proliferation and deletion, misfolded A\textsubscript{β} overload and ROS generation. This leads to the condition of mitochondrial dysfunction and to rescue the ailing cell UPR\textsuperscript{mt} is stimulated. The effect of mitochondrial dysfunction leads to development of neuropathologies associated with AD (Aliev et al., 2008, 2013; Onyango et al., 2016). as well as memory loss (Willette et al., 2015; Wijesekara et al., 2017). In addition, there is decline in key neuronal glucose transporters, GLUT1 and GLUT3, as shown in AD mouse models (Ding et al., 2013). The exact molecular mechanism underlying the effect of glucose uptake in AD model is not completely understood, but evidences suggest a close link between AD and insulin signaling. Apart from controlling glucose metabolism, insulin also regulates neural development with respect to learning and memory (Ying et al., 2017).

The lowering in glucose concentration due to lack of active transporters (GLUT1 and GLUT3) instates mitigating effect on hexosamine pathway (HBP), due to which O-GlcNAcylation is compromised with hyperphosphorylation on tau protein (Liu et al., 2009). XBPI(S) is shown to directly target the rate limiting enzyme of HBP, glutamine fructose-6-phosphate aminotransferase (GFAT1; Wang et al., 2014), as XBPI(S) transgenics showed rise in O-GlcNAcylation (Wang et al., 2014). The situation of insulin resistance established in aging has also been shown to increase HBP flux (Einstein et al., 2008). A gain-of-function mutation in GFAT1 of \textit{C. elegans} showed significant induction of ERAD and autophagy favoring longevity (Denzel et al., 2014).

Protein aggregation is a consequence of AD which is a result of abnormal proteostasis in the cell (Kaushik and Cuervo, 2015). An increase in the UPR\textsuperscript{ER} driven protein homeostasis was observed with the overexpression of GLUT1 as this promoted downregulation of expression of GRP78. GRP78, being the negative regulator of the UPR\textsuperscript{ER}, binds ATF6 and IRE1 thereby continuing them in an inactive state. One interesting study showed that flies (with increased glucose transport) when fed with the drug metformin showed mitigated levels of GRP78 with ensuing gain in lifespan, additionally the expression of GLUT1 and its association with the beginning of UPR\textsuperscript{ER} exerted neuroprotective effect (Niccoli et al., 2016).

**TARGETING UPR\textsuperscript{ER} TO MANAGE AD**

The involvement of ER stress and hence the UPR\textsuperscript{ER} in neuropathologies exposes the molecules of the pathway as attractive targets for therapeutic interventions. Here, we have

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**FIGURE 2** | Mitochondrial dysfunction in AD: various stress insults like aging and oxidative stress disrupt client protein folding in mitochondria thereby invoking mitochondrial UPR\textsuperscript{mt}. Numerous events line up; there is mitochondrial DNA (mtDNA) proliferation and deletion, misfolded A\textsubscript{β} overload and ROS generation. This leads to the condition of mitochondrial dysfunction and to rescue the ailing cell UPR\textsuperscript{mt} is stimulated. The effect of mitochondrial dysfunction leads to development of neuropathologies associated with AD (Aliev et al., 2008, 2013; Onyango et al., 2016).
compiled reports from studies that have targeted molecules of UPR\textsuperscript{ER} for managing the deterioration caused by AD (Figure 1).

**eIF2α and PERK in AD**

There are accumulating evidences that support increased phosphorylation of PERK and eIF2α in AD (Chang et al., 2002; Page et al., 2006; Kim et al., 2007). The processing of highly expressed single-pass transmembrane protein in brain, the amyloid precursor protein, leads to the generation of neurotoxic Aβ during neuropathogenesis. Reports suggest that the secretase β-site APP cleaving enzyme-1 (BACE1), increases APP cleavage as a result of eIF2α phosphorylation leading to the production of Aβ in neurons (O’Connor et al., 2008). The PERK tier of UPR when suppressed leads to the alleviation of synaptic plasticity and memory loss in AD (Ma et al., 2013). The administration of arctigenin, a bioactive product from *Arctium lappa* (L.), has been known to inhibit BACE1 translation through dephosphorylation of eIF2α-P (Zhu et al., 2013). The phosphorylation of eIF2α is central to integrated stress response (ISR) that modulates UPR (Harding et al., 2000b) and formation of memory proteins (Costa-Mattioli et al., 2005). ISR inhibitor (ISRIB) interferes with ISR by affecting eIF2β activity whose competitive inhibitor is eIF2α-P (Krishnamoorthy et al., 2001; Sekine et al., 2015; Bogorad et al., 2017). This comprehensively reverses the effect of eIF2α-P, which resulted in the restoration of translation and hence long term memory enhancement in rodents (Sidrauski et al., 2013, 2015). The genetic deletion of eIF2 kinases, PERK, GCN2 and dsRNA-dependent protein kinase (PKR) ameliorate synaptic plasticity and memory in AD models (Ma et al., 2013). The transient translational halt induced by PERK-P/eIF2α-P was challenged by GSK2606414, a PERK inhibitor, because of which tau phosphorylation could be checked, resulting in the amelioration of neurodegeneration (Axten et al., 2012; Radford et al., 2015). The development of AD manifested by Aβ accumulation forces tau hyper phosphorylation in sync with increased activity of glycogen synthase kinase-3β (GSK-3β) in the cortical neurons (Takashima et al., 1993, 1996; Tomidokoro et al., 2001; De Felice et al., 2008; Resende et al., 2008). Resende et al. (2008) showed that Aβ oligomers cause ER stress linked calcium leakage which in turn leads to GSK-3β activation, the later when inhibited by GSK-3β inhibitor I, led to the prevention of Aβ induced phosphorylation of tau.

**IRE1/XBP1 in AD**

The advantageous effects of XBP1 on memory was proven in neural-specific XBP1 knockout mice featuring impaired learning and synaptic plasticity deficit, where injections of adeno-associated viruses delivered XBP1(S) resulted in establishing long-term hippocampus memory (Martinez et al., 2016). In accordance with this finding, another study reinforced the neuroprotective role of XBP1 in AD mice (Casas-Tinto et al., 2011; Cisse et al., 2017). Nonetheless, a flavonol, called quercetin, activated endoribonuclease activity of IRE1 and inhibited tau hyperphosphorylation (de Boer et al., 2006; Suganthy et al., 2016). In cases of familial AD, deletions or mutations in presenilin genes accentuate ER Ca\textsuperscript{2+} leakage. The JNK inhibitor, SP600125, when challenged in PS1/PS2 double knockout mouse embryonic fibroblast, caused inhibition of Ca\textsuperscript{2+} leakage (Das et al., 2012). The neuroinflammation exhibited in AD through tau phosphorylation mediated by the kinase activity of JNK was inhibited by SP600125, consequently inhibiting Aβ-induced c-Jun phosphorylation (Vukic et al., 2009; Zhou et al., 2015).

**FUTURE DIRECTIONS AND CONCLUDING REMARKS**

ER, being a central organelle in nerve cells, coordinates with the cellular homeostasis by managing translation/modification of proteins and Ca\textsuperscript{2+} equilibrium, thereby maintains the proper signaling in brain. The disruption in neuronal physiology is quite evident in age-related AD where ER dysfunctions are prominently expressed in the form of imbalance in proteostasis. Advancements in studies based on AD models have clearly shown how we can intervene the molecular pillars of UPR\textsuperscript{ER} and its associated signaling cascades to manage neurodegeneration in age-related AD. The present review is an attempt to revise functional relevance of the studies conducted in the field of management of age-related AD through therapeutic interventions on the UPR\textsuperscript{ER} pathway and its associate’s molecules. Studies reinforce that the strategies where intervening the molecules, which are involved in transposing effects of aging on neurodegeneration, will cause reduction in probability of AD pathology. The manifestation of ER proteostasis is a direct indication of healthy nervous system. Progression in AD witnesses glucose hypo-metabolism in brain, reduction in glucose transporters in neurons and endothelial cells of blood brain barrier in direct proportion with the amount of neurofibrillary tangles. Type 2 diabetics with higher insulin resistance are at a greater risk of AD. Recent reports elucidate that managing UPR\textsuperscript{ER} can exert neuroprotective effect in AD (Smith and Mallucci, 2016). Additionally, as evidenced in the study by Sorrentino et al. (2017), the recapitulation of mitochondrial function through activation of UPR\textsuperscript{mt} can impede plaque formation. Aliev et al., also demonstrated link between cancer and AD where mtDNA over-proliferation and deletion induces cell cycle dysregulation prompting oncogenic pathway (Aliev et al., 2013). We have supporting literature that underpins the reversal of AD pathology by anticancer drugs (Cramer et al., 2012). Aiming at therapeutic intervention, the ailing mitochondria can be challenged with specific antioxidants like MitoQ, acetyl-L-carnitine and R-alpha lipoic acid to alleviate AD (Aliev et al., 2011; Volgyi et al., 2015). One remarkable study on astrocytes underpins the protective role of conditioned medium of human mesenchymal stem cells (CM-hMSCA) sourced from adipose tissue against neuropathologies (Baez-Jurado et al., 2017). The state of astrocyte mitochondrial dysfunction has been proven to be a start point for neuronal death (Baez et al., 2016). Pharmacological targeting of astrocytes has been proposed to be a potential way in therapeutics of AD (Baez et al.,...
2016). A transcriptomic analysis in astrocytes has put forward a conglomeration of various algorithms for strategic approaches in therapeutics of neuropathologies (Barreto et al., 2017).

We still need extensive and efficient model systems where the molecular intricacies of weakened UPR in aging-induced neuropathology in AD can be ventured upon, so that pharmacological as well as genetic tools could underscore the significance of UPR as well as UPR in aged brain.

REFERENCES

Acosta-Alvear, D., Zhou, Y., Blais, A., Tuikittis, M., Lents, N. H., Arias, C., et al. (2007). BXP1 controls diverse cell type- and condition-specific transcriptional regulatory networks. Mol. Cell. 27, 53–66. doi: 10.1016/j.molcel.2007.06.011

Alen, N. G., Gasimov, E., Obrenovich, M. E., Fischbach, K., Shenk, J. C., Smith, M. A., et al. (2008). Atherosclerotic lesions and mitochondria DNA deletions in brain microvessels: implication in the pathogenesis of Alzheimer’s disease. Vasc. Health Risk Manag. 4, 721–730. doi: 10.2147/vhrm.s2608

Aliev, G., Li, Y., Palacios, H. H., and Obrenovich, M. E. (2011). Oxidative stress induced mitochondrial DNA deletion as a hallmark for the drug development in the context of the cerebrovascular diseases. Recent Pat. Cardiovasc. Drug Discov. 6, 222–241. doi: 10.2174/157490191797376942

Aliev, G., Obrenovich, M. E., Tabrez, S., Jabir, N. R., Reddy, V. P., Li, Y., et al. (2013). Link between cancer and Alzheimer disease via oxidative stress induced by nitric oxide-dependent mitochondrial DNA overpoleration and deletion. Oxid. Med. Cell. Longev. 2013:962984. doi: 10.1155/2013/962984

Alzheimer’s Association. (2016). 2016 Alzheimer’s disease facts and figures.

Arnould, T., Michel, S., and Renard, P. (2015). Mitochondria retrograde signaling late-onset Alzheimer’s disease pathogenesis. J. Alzheimers Dis. 47, 33–47. doi: 10.3233/MCD-142110

Aksen, J. M., Medina, J. R., Feng, Y., Sha, A., Romeril, S. P., Grant, S. W., et al. (2012). Discovery of 7-methyl-5-[(3-trifluoromethy1)phenyl]acetyl-2,3-dihydro-1H-indol-5-yl]-7H-p yrrrolo[2,3-d]pyrimidin-4-amine (GSK6206641), a potent and selective first-in-class inhibitor of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK). J. Med. Chem. 55, 7193–7207. doi: 10.1021/jm300713s

Baez, E., Echeverria, V., Cabezas, R., Ávila-Rodriguez, M., Garcia-Segura, L. M., and Barreto, G. E. (2016). Protection by neuroglubin expression in brain pathologies. Front. Neurol. 7:146. doi: 10.3389/fneur.2016.00146

Baez-Jurado, E., Hidalgo-Lanussa, O., Guio-Vega, G., Ashraf, G. M., Echeverria, V., Aliev, G., et al. (2017). Conditioned medium of human adipose mesenchymal stem cells increases wound closure and protects human astrocytes following scratch assay in vitro. Mol. Neurobiol. doi: 10.1007/s12035-017-0771-4 [Epub ahead of print].

Barreto, G. E., Gomez, R. M., Bustos, R. H., Forero, D. A., Aliev, G., Tarasov, V. V., et al. (2017). Approaches of the transcriptomic analysis in astrocytes: potential pharmacological targets. Curr. Pharm. Des. 23, 4189–4197. doi: 10.2174/1381612823666170406113501

Baumeister, P., Luo, S., Skarnes, W. C., Sui, G., Seto, E., Shi, Y., et al. (2005). Endoplasmic reticulum stress induction of the Grp78/BiP promoter: activating mechanisms mediated by YY1 and its interactive chromatin modifiers. Mol. Cell. Biol. 25, 4529–4540. doi: 10.1128/mcb.25.11.4529-4540.2005

Bertolotti, A., Zhang, Y., Hendershot, L. M., Harding, H. P., and Ron, D. (2000). Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. Nat. Cell Biol. 2, 326–332. doi: 10.1038/35014014

Bogorad, A. M., Lin, K. Y., and Marintchev, A. (2017). Novel mechanisms of eIF2B action and regulation by eIF2α phosphorylation. Nucleic Acids Res. 45, 11962–11979. doi: 10.1093/nar/gks845

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De Felice, F. G., Wu, D., Lambert, M. P., Fernandez, S. J., Velasco, P. T., Lancer, P. N., et al. (2008). Alzheimer’s disease-type neuronal tau hyperphosphorylation induced by Aβ oligomers. Neurobiol. Aging 29, 1334–1347. doi: 10.1016/j.neurobiolaging.2007.02.029

Denzel, M. S., Storm, N. J., Gutschmidt, A., Baddi, R., Hinze, Y., Jarosch, E., et al. (2014). Hexosamine pathway metabolites enhance protein quality control and prolong life. Cell 156, 1167–1178. doi: 10.1016/j.cell.2014.01.061

Devi, L., and Ohno, M. (2013). Deletion of the eIF2α kinase GCN2 fails to rescue the memory decline associated with Alzheimer’s disease. PLoS One 8:e77335. doi: 10.1371/journal.pone.0077335

Devi, L., and Ohno, M. (2014). PERK mediates eIF2α phosphorylation responsible for BACE1 elevation, CREB dysfunction and neurodegeneration in a mouse model of Alzheimer’s disease. Neurobiol. Aging 35, 2272–2281. doi: 10.1016/j.neurobiolaging.2014.04.031

Ding, F., Yao, J., Rettberg, J. R., Chen, S., and Brinton, R. D. (2013). Early decline in glucose transport and metabolism precedes shift to ketogenic system in female aging and Alzheimer’s mouse brain: implication for bioenergetic intervention. PLoS One 8:e79977. doi: 10.1371/journal.pone.0079977

Einstein, F. H., Fishman, S., Bauman, J., Thompson, R. F., Huffman, D. M., Atzman, G., et al. (2008). Enhanced activation of a “nutrient-sensing” pathway with age contributes to insulin resistance. FASEB J. 22, 3450–3457. doi: 10.1096/f10-09041

Ellgaard, L., and Helenius, A. (2003). Quality control in the endoplasmic reticulum. Nat. Rev. Mol. Cell Biol. 4, 181–191. doi: 10.1038/nrm1052

Fiest, K. M., Roberts, J. I., Maxwell, C. J., Hogan, D. R., Smith, E. E., Frolkis, A., Adams, C. M., et al. (2016). Transcription factor ATF4 directs basal and stress-induced gene expression in the unfolded protein response and cholesterol extracellular proteostasis. Mol. Biol. Cell 27, 1536–1551. doi: 10.1091/mbc.E16-01-0039

Fonseca, A. C., Ferreiro, E., Oliveira, C. R., Cardoso, S. M., and Pereira, C. F. (2013). Activation of the endoplasmic reticulum stress response by the amyloid-β 1–40 peptide in brain endothelial cells. Biochim. Biophys. Acta 1832, 2191–2203. doi: 10.1016/j.bbadis.2013.08.007

Fusakio, M. E., Willy, J. A., Wang, Y., Mirek, E. T., Al Baghdadi, R. J., Adams, C. M., et al. (2016). Transcription factor ATF4 directs basal and stress-induced gene expression in the unfolded protein response and cholesterol metabolism in the liver. Mol. Biol. Cell 27, 1536–1551. doi: 10.1091/mbc.E16-01-0039

Genereux, J. C., Qu, S., Zhou, M., Ryno, L. M., Wang, S., Shoulders, M. D., et al. (2015). Unfolded protein response-induced ERdj3 secretion links ER stress to extracellular proteostasis. EMBO J. 34, 4–19. doi: 10.15252/embj.201448896

Gourmaud, S., Paquet, C., Dumurgier, J., Pace, C., Bouras, C., Gray, F., et al. (2015). Increased levels of cerebrospinal fluid JNK3 associated with amyloid pathology: links to cognitive decline. J. Psychiatry Neurosci. 40, 151–161. doi: 10.1503/jpn.140062

Haase, C., and Selkoe, D. J. (2007). Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer’s amyloid β-peptide. Nat. Rev. Mol. Cell Biol. 8, 101–112. doi: 10.1038/nm2101

Halliday, M., and Mallucci, G. R. (2015). Modulating the unfolded protein response to prevent neurodegeneration and enhance memory. Neuropathol. Appl. Neurobiol. 41, 414–427. doi: 10.1111/nan.12211

Hamos, J. E., Oblas, B., Pulski-Salo, D., Welch, W. J., Bole, D. G., and Drachman, D. A. (1991). Expression of heat shock proteins in Alzheimer’s disease. Neurology 41, 345–350. doi: 10.1223/WNL.41.3.345

Han, J., Back, S. H., Hur, J., Lin, Y.-H., Gildersleeve, R., Shan, J., et al. (2013). ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death. Nat. Cell Biol. 15, 481–490. doi: 10.1038/ncb2738

Harding, H. P., Novoa, I., Zhang, Y., Zeng, H., Wek, R., Schapira, M., et al. (2000a). Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol. Cell 6, 1099–1108. doi: 10.1016/s1097-2765(00)01008-8

Harding, H. P., Zhang, Y., Bertolotti, A., Zeng, H., and Ron, D. (2000b). Perk is essential for translational regulation and cell survival during the unfolded protein response. Mol. Cell 5, 897–904. doi: 10.1016/s1097-2765(00)00303-5

Harding, H. P., Zhang, Y., and Ron, D. (1999). Protein translation and folding are coupled by an endoplasmic reticulum-resident kinase. Nature 397, 271–274. doi: 10.1038/16739

Harding, H. P., Zhang, Y., Zeng, H., Novoa, I., Lu, P. D., Calnon, M., et al. (2003). An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. Mol. Cell 11, 619–633. doi: 10.1016/s1097-2765(03)00105-9
and tau pathology in Alzheimer’s disease. *Brain* **132**, 1820–1832. doi: 10.1093/brain/awp099

Loewen, C. A., and Feany, M. B. (2010). The unfolded protein response protects from tau neurotoxicity in vivo. *PLoS One* **5**(11):e13084. doi: 10.1371/journal.pone.0013084

Lourenço, M. V., Clarke, J. R., Frozza, R. L., Bomfim, T. R., Forný-Gernando, L., Batista, A. F., et al. (2013). TNF-α mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer’s β-amyloid oligomers in mice and monkeys. *Cell Metab.* **18**, 831–843. doi: 10.1016/j.cmet.2013.11.002

Ma, T., Trinh, M. A., Wexler, A. J., Bourbon, C., Gatti, E., Pierre, P., et al. (2013). Suppression of eIF2α kinase alleviates Alzheimer’s disease-related plasticity and memory deficits. *Nat. Neurosci.* **16**, 1299–1305. doi: 10.1038/nn.3486

Ma, K., Vattem, K. M., and Wek, R. C. (2002). Dimerization and release of enzyme activities of chaperones PDI and BiP in aged mouse livers. *J. Biol. Chem.* **277**, 18728–18735. doi: 10.1074/jbc.M200903200

Marciniak, S. J., García-Bonilla, L., Hu, J., Harding, H. P., and Ron, D. (2006). Activation-dependent substrate recruitment by the eukaryotic translation initiation factor 2 kinase PERK. *J. Cell Biol.* **172**, 201–209. doi: 10.1083/jcb.200508099

Marciniak, S. J., Yun, C. Y., Oyadomari, S., Novoa, I., Zhang, Y., Jungreis, R., et al. (2004). CHOP induces death by promoting protein synthesis and ER stress regulation on the molecular modality of breast cancer. *Cell Death Differ.* **11**, 1382–1394. doi: 10.1038/sj.cdd.4401216

Minakshi, R., Rahman, S., Jan, A. T., Archana, A., and Kim, J. (2017). Implications of aging and the endoplasmic reticulum unfolded protein response on the molecular pathology of breast cancer. *Exp. Mol. Med.* **49**:e389. doi: 10.1038/emmm.2017.215

Minter, M. R., Taylor, J. M., and Crack, P. J. (2016). The contribution of neuroinflammation to amyloid toxicity in Alzheimer’s disease. *J. Neurochem.* **136**, 457–474. doi: 10.1111/jnc.13411

Moneim, A. E. (2015). Oxidant/Antioxidant imbalance and the risk of Alzheimer’s disease. *Curr. Alzheimer Res.* **12**, 335–349. doi: 10.2174/156720501266510325182702

Mori, K. (2009). Signalling pathways in the unfolded protein response: development from yeast to mammals. *J. Biochem.* **146**, 743–750. doi: 10.1093/jb/mvp166

Mosconi, L., Brys, M., Switalski, R., Mistur, R., Glodzik, L., Pirraglia, E., et al. (2008). Phosphorylation of the translation initiation factor eIF2α in response to endoplasmic reticulum stress. *J. Biol. Chem.* **283**, 10640–10647. doi: 10.1074/jbc.M706363200

Naidoo, N., Rahman, S., Jan, A. T., Archana, A., and Kim, J. (2017). Activation-dependent substrate recruitment by the eukaryotic translation initiation factor 2 kinase PERK. *J. Cell Biol.* **172**, 201–209. doi: 10.1083/jcb.200508099

Ohno, M. (2014). Roles of eIF2α kinases in the pathogenesis of Alzheimer’s disease. *Front. Mol. Neurosci.* **7**:22. doi: 10.3389/fnmol.2014.00022

Onuki, R., Bando, Y., Suyama, E., Katayama, T., Kawasumi, H., Baba, T., et al. (2004). An RNA-dependent protein kinase is involved in tunicamycin-induced apoptosis and Alzheimer’s disease. *EMBO J.* **23**, 959–968. doi: 10.1038/sj.emboj.7600049

Onyango, P., Celik, I., McCaffery, J. M., Boeke, J. D., and Feinberg, A. P. (2002). SIRT3, a human SIR2 homologue, is an NAD-dependent deacetylase localized to mitochondria. *Proc. Natl. Acad. Sci. U S A* **99**, 13653–13658. doi: 10.1073/pnas.222538099

Onyango, I. G., Dennis, J., and Khan, S. M. (2016). Mitochondrial dysfunction in Alzheimer’s disease and the rationale for bioenergetics based therapies. *Aging Dis.* **7**, 201–214. doi: 10.14336/AD.2015.1007

Page, G., Rioux Bilan, A., Ingrand, S., Lafay-Chebassier, C., Pain, S., Perault Pochat, M. C., et al. (2006). Activated double-stranded RNA-dependent protein kinase and neuronal death in models of Alzheimer’s disease. *Neuroscience* **139**, 1343–1354. doi: 10.1016/j.neuroscience.2006.01.047

Paz Gavilán, M., Vela, J., Castaño, A., Ramos, B., del Río, J. C., Vitorica, J., et al. (2006). Cellular environment facilitates protein accumulation in aged rat hippocampus. *Neurobiol. Aging* **27**, 973–982. doi: 10.1016/j.neurobiolaging.2005.05.010

Rabek, J. P., Boylston, W. H. III., and Papacostas, G. (2001). Mitochondrial dysfunction in neurodegenerative diseases: a neuropathological perspective. *Nat. Neurosci.* **4**, 2091–2099. doi: 10.1002/jnr.21648

Ravel, E., Gilbert, T., Roche, S., Drai, J., Blond, E., Eccehard, R., et al. (2015). Influence of oxidative stress biomarkers on cognitive decline. *J. Alzheimers Dis.* **45**, 553–560. doi: 10.3233/JAD-141797

Romero-Ramirez, L., Cao, H., Nelson, D., Hammond, E., Lee, A. H., Yoshida, H., et al. (2004). XBP1 is essential for survival under hypoxic conditions and is required for tumor growth. *Cancer Res.* **64**, 5943–5947. doi: 10.1158/0008-5472. can-04-1606

Sam, A., Rahman, S., Kumar, V., Zaidi, S., Islam, A., Ali, S., et al. (2017). Protein aggregation, misfolding and consequential human neurodegenerative diseases. *Int. J. Neurosci.* **127**, 1047–1057. doi: 10.1080/00207454.2017.1286339

Shelgren, P., Bloomow, K., Bretelet, M. M., de Stooper, B., Frisoni, G. B., Salloway, S., et al. (2016). Alzheimer’s disease. *Lancet* **388**, 505–517. doi: 10.1016/S0140-6736(15)01244-1

Sepehr, W., and Hoozemans, J. J. (2015). The unfolded protein response in neurodegenerative diseases: a neuropathological perspective. *Acta Neuropathol.* **130**, 315–331. doi: 10.1007/s00401-015-1462-8

Schröder, M., and Kaufman, R. J. (2005). The mammalian unfolded protein response: a neurobiological view. *Brain* **128**, 1820–1831. doi: 10.1093/brain/awr210

Scheper, W., and Hoozemans, J. J. (2015). The unfolded protein response in neurodegenerative diseases: a neuropathological perspective. *Acta Neuropathol.* **130**, 315–331. doi: 10.1007/s00401-015-1462-8

Selkoe, D. J. (2001a). Alzheimer’s disease results from the cerebral accumulation and cytotoxicity of amyloid β-protein. *J. Alzheimers Dis.* **3**, 75–80. doi: 10.3233/JAD-2001-015

Selkoe, D. J. (2001b). Alzheimer’s disease: genes, proteins, and therapy. *Physiol. Rev.* **81**, 741–766. doi: 10.1152/physrev.2001.81.2.741

Selkoe, D. J. (2004a). Alzheimer disease: mechanistic understanding predicts novel therapies. *Ann. Intern. Med.* **140**, 627–638. doi: 10.1003/journal.pone.2014.0002420-00047

Selkoe, D. J. (2004b). Cell biology of protein misfolding: the examples of Alzheimer’s and Parkinson’s diseases. *Nat. Cell Biol.* **6**, 1054–1061. doi: 10.1038/ncl1014-1054

Shen, J., Chen, X., Hendershot, L., and Prywes, R. (2002). ER stress regulation of ATF6 localization by dissociation of Bip/GRP78 binding and unmasking
of Golgi localization signals. Dev. Cell 3, 99–111. doi: 10.1016/s1534-5807(02)00203-4
Sohji, M., Iwakami, N., Takeuchi, S., Varagić, M., Suzuki, M., Kanazawa, I., et al. (2000). JNK activation is associated with intracellular β-amyloid accumulation. Brain Res. Mol Brain Res. 85, 221–233. doi: 10.1016/s0169-328x(00)00245-x
Shoulders, M. D., Ryno, L. M., Generex, J. C., MoreSCO, J. J., Tu, P. G., Wu, C., et al. (2013). Stress-independent activation of XBP1s and/or ATf6 reveals three functionally diverse ER proteostasis environments. Cell Rep. 3, 1279–1292. doi: 10.1016/j.celrep.2013.03.024
Sidrascui, C., Acosta-Alvear, D., Khoutorsky, A., Vedantham, P., HeeRN, B. R., Li, H., et al. (2013). Pharmacological brake-release of mRNA translation enhances cognitive memory. Elife 2:e00498. doi: 10.7554/eLife.00498
Sidrascui, C., McGeachy, A. M., Ingolia, N. T., and Walter, P. (2015). The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly. Elife 4:e05330. doi: 10.7554/eLife.05330
Smith, H. L., and Mallucci, G. R. (2016). The unfolded protein response: mechanisms and therapy of neurodegeneration. Brain 139, 2113–2121. doi: 10.1093/brain/aww101
Someya, S., Yu, W., Hal lows, W. C., Xu, J., Vann, J. M., Leeuwenburgh, C., et al. (2010). Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. Cell 143, 802–812. doi: 10.1016/j.cell.2010.10.002
Sorrentino, V., Romani, M., Mouchiroud, L., Beck, J. S., Zhang, H., D’Amico, D., Shoji, M., Iwakami, N., Takeuchi, S., Waragai, M., Suzuki, M., Kanazawa, I., et al. (2010). The dysregulation of intracellular calcium of tau protein kinase I/glycogen synthase kinase-3 protein kinase I is essential for amyloid-β-protein-induced neurotoxicity. J. Biol. Chem. 285, 33449–33458. doi: 10.1074/jbc.m110.144047
Urano, F., Wang, X., Bertolotti, A., Nakamura, Y., Chen, J., Chen, L., et al. (2013). Arctigenin enhances cognitive memory. J. Neurosci. 33, 1081–1086. doi: 10.1523/JNEUROSCI.4790-12.2013
Wang, Z. V., Deng, Y., Gao, N., Pedrozo, Z., Li, D. L., Morales, C. R., et al. (2014). Spliced X-box binding protein 1 couples the unfolded protein response to hexosamine biosynthetic pathway. Cell 156, 1179–1192. doi: 10.1016/j.cell.2014.01.014
Wang, W., Yin, J., Ma, X., Zhao, F., Siedlik, S. L., Wang, Z., et al. (2017). Inhibition of mitochondrial fragmentation protects against Alzheimer’s disease in rodent model. Hum. Mol. Genet. 26, 4118–4131. doi: 10.1093/hmg/ddx299
Wijesekara, N., Ahrens, R., Sabale, M., Wu, L., Ha, K., Verdile, G., et al. (2017). Amyloid-β and islet amyloid pathologies link Alzheimer disease and type 2 diabetes in a transgenic model. FASEB J. 31, 5409–5418. doi: 10.1096/fj. 201704318
Willette, A. A., Bendlin, B. B., Starks, E. J., Birdsell, A. C., Johnson, S. C., Christian, B. T., et al. (2015). Association of insulin resistance with cerebral glucose uptake in late middle-aged adults at risk for Alzheimer disease. JAMA Neurol. 72, 1013–1020. doi: 10.1001/jamaneurol.2015.0613
Yamamoto, K., Sato, T., Matsui, T., Sato, M., Okada, T., Yoshida, H., et al. (2007). Transcriptional induction of mammalian ER Q15a control protein controls is mediated by single or combined action of ATF6α and XBP1. Dev. Cell 13, 365–376. doi: 10.1016/j.devcel.2007.07.018
Ying, M., Sai, X., Zhang, Y., Sun, Q., Qi, Z., Luo, X., et al. (2017). Identification of novel key molecules involved in spatial memory impairment in triple transgenic mice of Alzheimer’s disease. Mol. Neurobiol. 54, 3843–3858. doi: 10.1007/s12035-016-9955-2
Yoon, S. S., and Jo, S. A. (2012). Mechanisms of amyloid-β peptide clearance: potential therapeutic targets for Alzheimer’s disease. Biomed. Ther. (Seoul) 20, 245–255. doi: 10.4062/biomolther.2012.20.3.245
Yoshida, H., Haze, K., Yanagi, H., Yura, T., and M0ri, K. (1998). Identification of the cis-acting endoplasmic reticulum stress response element responsible for transcriptional induction of mammalian glucose-regulated proteins. Involvement of basic leucine zipper transcription factors. J. Biol. Chem. 273, 33741–33749. doi: 10.1074/jbc.273.50.33741
Yoshida, H., Matsui, T., Hosokawa, N., Kaufman, R. J., Nagata, K., and Mori, K. (2003). A time-dependent phase shift in the mammalian unfolded protein response. Dev. Cell 4, 265–271. doi: 10.1016/s1534-5807(03)00022-4
Yoshida, H., Matsui, T., Yamamoto, A., Okada, T., and Mori, K. (2001). Expression of inflammatory genes induced by β-amyloidosis induces the initial stage of tau accumulation in APPswe/PS1dE9 mice. Cell. Biol. 153, 1435–1447. doi: 10.1016/s0006-3495(96)79570-x
Taylor, R. C., and DunILL, A. (2013). XBP-1 is a cell-nonautonomous regulator of stress resistance and longevity. Cell 153, 1435–1447. doi: 10.1016/j.cell.2013.05.042
Tirasophon, W., Weihinda, A. A., and Kaufman, R. J. (1998). A stress response pathway from the endoplasmic reticulum to the nucleus requires a novel bifunctional protein kinase/endoribonuclease (IRE1p) in mammalian cells. Genes Dev. 12, 1812–1824. doi: 10.1101/gad.12.12.1812
Tomidokoro, Y., Ishiguro, K., Harigaya, Y., Matsubara, E., Ikeda, M., Park, J. M., et al. (2001). Apo amyloidosis induces the initial stage of tau accumulation in APP(Sw) mice. Neurosci. Lett. 299, 169–172. doi: 10.1016/s0304-3900(01)00767-5
Urano, F., Wang, X., Bertolotti, A., Zhang, Y., Chung, P., Harding, H. P., et al. (2000). Coupling of stress in the ER to activation of JNK protein kinase I and mitochondria (M'T) in Alzheimer’s disease: the role of the ER-MT cross-talk. Curr. Alzheimer Res. 12, 655–672. doi: 10.2174/156720501266616507010095035
Vukic, V., Callaghan, D., Walker, D., Lue, F. L., Liu, Q. Y., Couraud, P. O., et al. (2009). Expression of inflammatory genes induced by β-amyloid peptides in human brain endothelial cells and in Alzheimer’s brain is mediated by the JNK-AP1 signaling pathway. Neurobiol. Dis. 34, 95–106. doi: 10.1016/j.nbd. 2008.12.007
Walter, P., and Ron, D. (2011). The unfolded protein response: from stress pathway to homeostatic regulation. Science 334, 1081–1086. doi: 10.1126/science.1209938
Wang, Z. V., Deng, Y., Gao, N., Pedrozo, Z., Li, D. L., Morales, C. R., et al. (2014). Spliced X-box binding protein 1 couples the unfolded protein response to hexosamine biosynthetic pathway. Cell 156, 1179–1192. doi: 10.1016/j.cell.2014.01.014
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