Forum Minireview

Molecular Approaches to the Treatment, Prophylaxis, and Diagnosis of Alzheimer's Disease:**Endoplasmic Reticulum Stress and Immunological Stress in Pathogenesis of Alzheimer's Disease**Toru Hosoi^{1,*a} and Koichiro Ozawa^{1,*b}¹Department of Pharmacotherapy, Graduate School of Biomedical Sciences, Hiroshima University,
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Abstract. Alzheimer's disease (AD) is an age-related neurodegenerative disorder, accompanied by neuronal loss and the formation of senile plaques in the brain. Glial cells, such as microglia, have been shown to be activated and induce chronic inflammatory responses in AD brain. The endoplasmic reticulum (ER) functions to facilitate protein folding. However, ER stress occurs when cells are exposed to stress. Mounting evidence suggests that ER stress is involved in the pathology of AD. Meanwhile, recent findings suggested crosstalk between ER stress and immune function. However, the mechanisms linking the progression of AD with ER and immunological stress are still not clear. In the present paper, we review and discuss recent results regarding the mechanism of AD pathogenesis, focusing on ER stress and immunological stress.

Keywords: endoplasmic reticulum stress, inflammation, glial cell, neuron, Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is characterized by a decline in cognitive function (1), which is accompanied by neuronal loss and senile plaques in the brain. In addition to these hallmarks, new diagnostic method for imaging AD pathology using novel PET/SPECT probes has been recently developed (for details, see the article written by Ono and Saji in this Forum Minireview series: Ref. 2). Neuropathological analyses of AD brain suggest one of the major causes of AD to be the accumulation of amyloid β -peptide in cerebral neuritic plaques. The build-up of amyloid β -peptide has been suggested to activate glial cells, such as microglia and astrocytes (for details, see the article written by Takata and Kitamura in this Forum Minireview series: Ref. 3), which subsequently activate immune reactions. Moreover, increase in amyloid β -peptide would result in neuronal cell death in the affected areas. Interestingly, cell death has been suggested

to accompany endoplasmic reticulum (ER) stress (4, 5). The ER is an organelle that functions to facilitate protein folding. However, exposure to stress results in loss of function and causes ER stress. Intriguingly, crosstalk between ER stress and immune function has been suggested (6 – 11). Therefore, elucidation of the mechanisms of ER stress and immune function activated in AD brain may provide beneficial information for the pharmacological treatment of AD. Thus, in this review, we describe basic mechanisms of ER and immunological stress and discuss the therapeutic opportunities for AD.

2. ER stress

The accumulation of unfolded or misfolded proteins in the ER triggers ER stress. Cells counteract the stress by activating several sensor proteins located in the ER (Fig. 1). This process is known as the unfolded protein response (UPR). Activation of UPR alleviates ER stress by 1) increasing the folding capacity of unfolded or misfolded proteins, 2) inhibiting general protein translation, and 3) promoting the degradation of unfolded or misfolded proteins (12 – 14). In addition, unfolded or misfolded proteins in the ER are retrogradely transported

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Fig. 1. Mechanisms of the integrative signaling response to ER stress. Upon ER stress, several ER-localized stress-sensor proteins are activated, which subsequently induces a subset of ER stress-regulated genes. In addition, ER stress promotes the degradation of unfolded or misfolded proteins.

from the ER to the cytoplasm through translocons, which are then degraded by the ubiquitin–proteasome system (for details, see the article written by Kaneko et al. in this Forum Minireview series: Ref. 15) (16, 17). On the other hand, when exposed to stronger or prolonged stress, which cells by themselves cannot withstand, cells will eventually undergo apoptosis through the activation of ER-specific caspases (18, 19) or apoptotic transcription factors, such as CCAAT/enhancer-binding protein homologous protein (CHOP) (20, 21).

Three major types of ER-resident proteins have been identified as sensors for ER stress: that is, inositol-requiring protein-1 (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6). When these stress-sensor proteins are activated through the sensing of unfolded proteins in the ER, it will eventually transmit the signals to nucleus and increases a subset of specific genes to accommodate such stress (22).

Activation of IRE1 induces X-box binding protein 1 (XBP-1) mRNA splicing by cleaving off its intron (23). Spliced XBP-1 then functions as a transcription factor specific for ER stress-related genes (24).

Activation of PERK phosphorylates the α -subunit of eukaryotic translation initiation factor 2 (eIF2), which results in translational repression (25, 26). eIF2 phosphorylation, however, promotes the translation of activating transcription factor 4 (ATF4), which subsequently produces CHOP protein, an apoptotic transcription factor (27).

Activation of ATF6 is mediated through regulated intramembrane proteolysis (RIP), which involves translocation from the ER to the Golgi complex, the site where it is cleaved by Golgi-resident serine proteases, site 1 protease (S1P), and site 2 protease (S2P) (28, 29). The cleaved 50-kDa cytoplasmic basic-leucine zipper (b-ZIP)-containing fragment then activates the transcription of UPR target genes.

3. Alzheimer's disease and ER stress

AD is characterized by an accumulation of unfolded or misfolded proteins in the brain. Several reports indicate the activation of UPR in AD brain (30 – 32), suggesting a possible link between AD and ER stress. One of the proposed mechanisms of AD progression is the accumulation of amyloid β -peptide in cerebral neuritic plaques. Amyloid β activates UPR signaling such as PERK or XBP-1 splicing, which in turn is suggested to prevent amyloid β neurotoxicity (33, 34). Amyloid β -peptide is generated by cleavage of amyloid precursor protein (APP). Presenilin-1 (PS1) and β -site APP cleaving enzyme-1 (BACE1) are important components of γ -secretase- and β -secretase-mediated cleavage of APP, respectively. Several types of familial gene variations have been suggested to be linked with AD pathology (for details, see the article written by Shoji in this Forum Minireview series: Ref. 35). Interestingly, a familial AD-linked PS1 mutation has been shown to be associated

with ER stress (36), and eIF2 α phosphorylation was shown to increase BACE1 levels (37). Moreover, amyloid β -peptide-induced neuronal cell death was mediated through ER stress-specific mouse caspase-12 (18) or human caspase-4 (19). In addition, *S*-nitrosylation of protein-disulphide isomerase (PDI), an ER-localized protein involved in disulfide bonds, was reported to be involved in protein misfolding and neurodegeneration in cases of sporadic AD (38). PDI has been suggested to attenuate protein misfolding in neurodegenerative disease. In this report, they suggested that formation of *S*-nitrosylated PDI (SNO-PDI) would cause malfunction of PDI, which would result in neurodegenerative disease. As nitric oxide (NO) is involved in AD progression (39), the linkage of NO and ER stress on the development of sporadic AD would be a mechanism involved. On the other hand, an alternatively spliced form of the PS2 gene, which lacks exon 5 (PS2V), has been reported to be expressed in sporadic AD brains (40), and the cells expressing PS2V were found to be more susceptible to ER stresses (41). Therefore, the linkage between PS2V and ER stress would be one of the causal factors for sporadic AD. Previously, we reported that serine/threonine kinase Akt, a downstream target of PI3K, is regulated by ER stress in glial cells (42). We found that Akt expression was transiently up-regulated, but down-regulated in response to ER stress. In addition, one possible mechanism of Akt regulation would be through TEK/Tie2 expression because the levels were regulated by ER stress (43). Increased activation of Akt was observed in AD brains (44–46). Meanwhile, weak activation of Akt was found in terminally degenerated AD neurons (46). PI3K/Akt signaling regulates cell survival. Indeed, deactivation of Akt in ER-stressed cells caused cell death (47, 48). Therefore, ER stress would regulate the activation status of Akt, which may be linked with the neurodegeneration observed in AD.

Overall, these molecular and pathological findings suggest that ER stress may be involved in the progression of AD.

4. Crosstalk between ER stress and immunological stress

In addition to ER stress, inflammatory genes are up-regulated in AD brain. Moreover, it is believed that inflammatory processes are involved in the development of sporadic AD (49). Therefore, chronic inflammatory conditions would contribute to the disease. Emerging evidence suggests that in addition to neuronal cells, glial cells such as microglia and astrocytes participate in AD progression. For example, amyloid β accumulation activates glial cells, which subsequently produce pro-inflam-

matory cytokines and inducible nitric oxide synthase (iNOS) (50–52). These inflammatory responses in the glial cells in turn affect neuronal cell fate. Therefore, it is possible that such neuro-glial crosstalk would contribute to AD. On the other hand, the existence of crosstalk between ER stress and immune function has been suggested (6–11). The transcription factor XBP-1 has been reported to induce interleukin (IL)-6 expression in B cells (6), and ER stress elicited an acute inflammatory response through the liver-specific transcription factor CREBH (9). Meanwhile, ER stress-induced CHOP expression was suppressed by prior activation of toll-like receptor (TLR) 3 or 4, which recognizes specific molecular patterns of microbial components (10). Conversely, activation of the immune system has been shown to increase UPR. Lipopolysaccharide (LPS), a Gram-negative bacterial cell wall component, induced the UPR-regulated expression of genes such as CHOP in lung (7). Moreover, TLR activated IRE1 α -XBP1 signaling and TLR-activated XBP1 was required for optimal and sustained production of pro-inflammatory cytokines in macrophages (11). In addition, the pro-inflammatory cytokine tumor necrosis factor α (TNF α) itself has been shown to induce UPR (8) and interferon- γ -induced apoptosis of oligodendrocytes was mediated through ER stress (53).

Overall, taking into account the functional crosstalk between ER stress and immune function, these factors may play key roles in the progression of AD. However, it is not clear whether ER stress-immune crosstalk is observed in the AD brain.

5. Concluding remarks

In recent years, research into the basic mechanisms of UPR and ER stress-related diseases has progressed rapidly. Importantly, in addition to AD, involvement of ER stress in Parkinson's disease, cerebral ischemic insult, cancer, obesity, and diabetes has been suggested. These observations open possibilities for developing novel therapeutic compounds that can ameliorate ER stress. Indeed, there have been reports of several compounds that can target ER stress-regulated proteins such as eIF2 α (54), IRE1 (55–57), and GRP78 (58). In addition, small molecules known as chemical chaperones, which inhibit the aggregation of proteins, were shown to be effective in reducing ER stress and ameliorating Parkinson's disease (59), diabetes (60), and obesity (61, 62).

Epidemiological evidence suggests that non-steroidal anti-inflammatory drugs (NSAIDs) would be useful for treating AD (63). The pharmacological action of NSAIDs against AD would be mediated by attenuating inflammation. Intriguingly, some NSAIDs were shown to modulate ER stress in neuronal (64) as well as glial cells (65).

These results raise the possibility that several NSAIDs may have unique pharmacological properties in regulating ER stress. Therefore, we speculate that the multifunctional properties of NSAIDs, that is, attenuating ER stress as well as immunological stress, would result in beneficial effects in attenuating AD. However, these possibilities require further analysis.

In addition to regulating ER stress, several reports suggest the physiological role of each component of UPR. It is suggested that each branch of the UPR components have a diverse and specific role for the normal functions of cellular homeostasis (66–70). Therefore, NSAIDs as well as compounds that can regulate ER stress by regulating UPR would affect basal physiologic actions. Such a pharmacological action may, in turn, cause side effects. Thus, special attention is required for discovery and use of new drugs targeting UPR.

Although pharmacological research into ER stress is still in its infancy, we believe that analyzing the mechanisms involved and identifying compounds directed against ER stress will provide new avenues for treating AD.

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