



ER stress signaling and neurodegeneration: At the intersection between Alzheimer's disease and Prion-related disorders



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ARTICLE INFO

Article history:

Available online 31 December 2014

Keywords:

Prion-like diseases

Amyloid formation

Unfolded protein response (UPR)

ER-stress

Sustained translational repression

Targeting ER-stress

ABSTRACT

Alzheimer's and Prion diseases are two neurodegenerative conditions sharing different pathophysiological characteristics. Disease symptoms are associated with the abnormal accumulation of protein aggregates, which are generated by the misfolding and oligomerization of specific proteins. Recent functional studies uncovered a key role of endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) in the occurrence of synaptic dysfunction and neurodegeneration in Prion-related disorders and Alzheimer's disease. Here we review common pathological features of both diseases, emphasizing the link between amyloid formation, its pathogenesis and alterations in ER proteostasis. The potential benefits of targeting the UPR as a therapeutic strategy is also discussed.

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1. Introduction

Efficient folding and quality control of proteins are required to sustain biological function in the cell. Abnormal protein aggregation is extensively associated with distinct pathological conditions, collectively known as protein misfolding disorders (PMDs) (Chiti and Dobson, 2006). PMDs include several cerebral and systemic amyloid diseases such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, type-2 diabetes and transmissible spongiform encephalopathies or Prion-related Diseases (PrD) (Dobson, 2002; Soto, 2003). While AD is the most common form of dementia and affects more than 25 million individuals worldwide, PrDs are rare diseases, affecting on average one person per million people. Although the incidence and clinical characteristics between AD and PrD are different, both conditions are characterized by the misfolding and aggregation of specific proteins and share clinical and pathological features including neuronal loss, progressive cog-

nitive decline and death (Braak and Braak, 1991; Prusiner, 1998). The major histopathological hallmarks of AD are the presence of amyloid plaques and neurofibrillary tangles (NFT) in the brain. Amyloid plaques are generated by the misfolding and extracellular deposition of a 42-residue peptide known as amyloid- β ($A\beta$), which is generated by the sequential cleavage of the amyloid precursor protein (APP) by β - and γ -secretases (Hardy and Selkoe, 2002). Creutzfeldt–Jacob disease (CJD) is the most common form of PrD. CJD involves the accumulation of a misfolded and protease-resistant form of the prion protein (PrP), and it is characterized by the spongiform degeneration of the brain, neuronal loss, and gliosis (Prusiner, 1998). An outstanding feature of PrDs is the mechanism of disease propagation: misfolded PrP is capable of spreading through the formation of self-propagating β -sheet-rich conformations of PrP (Prusiner, 1982). Recent evidence suggests that this intriguing form of transmission, initially described in PrD, may also occur in many neurodegenerative disorders including AD (Eisele et al., 2010; Kane et al., 2000; Langer et al., 2011; Meyer-Luehmann et al., 2006; Morales et al., 2011; Walker et al., 2002; Watts et al., 2014), which implies that a common pathological principle may underlie the progression and propagation of the pathology in both diseases (Soto, 2012). Accumulating evidence indicate that alterations in protein homeostasis (referred to as proteostasis) may underlie the progressive synaptic dysfunction in AD and PrDs,

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culminating in neuronal loss and irreversible brain damage (reviewed in [Hetz and Mollereau, 2014](#)). Therefore, understanding how the proteostasis network contributes to neurodegeneration represents an interesting target for disease treatment and prevention.

In addition to operating as a key compartment for protein folding and secretion, the ER is essential for maintaining proteostasis and buffer alterations in protein folding and synthesis. Several physiological and pathological conditions can perturb the protein folding process at the ER, where we highlight abnormalities in protein maturation, ER calcium homeostasis, ER-to-Golgi vesicular trafficking, or expression of certain mutant proteins ([Walter and Ron, 2011](#)). These conditions often lead to the accumulation of misfolded proteins in the ER lumen, giving rise to cellular condition referred to as “ER stress”. Under ER stress, cells activate an adaptive response, the unfolded protein response (UPR), that increases overall protein-folding capacity, in addition to enhancing the efficiency of quality control and protein degradation mechanisms to reduce the unfolded protein load ([Walter and Ron, 2011](#)). Under chronic or irreversible stress conditions the UPR shifts its signaling toward cell death mechanisms by activating complex pro-apoptotic programs ([Urrea et al., 2013](#)). The UPR is mediated by specialized stress sensors located at the ER membrane, which include inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK). Each stress sensor controls a downstream transcription factor that induces the expression of a subset of partially overlapping target genes involved in stress adaptation or apoptosis. In the case of IRE1, its endoribonuclease activity catalyzes the unconventional splicing of the mRNA encoding the transcription factor X-box binding protein (XBP1), which induces genes related to protein folding, protein degradation, lipid synthesis and others ([Acosta-Alvear et al., 2007](#); [Lee et al., 2003](#)). In addition, IRE1 can degrade specific mRNAs through IRE1-dependent decay (RIDD) ([Hollien et al., 2009](#)), and activate kinases such as JUN amino-terminal kinase (JNK) and the apoptosis signal-regulating kinase 1 (ASK1) ([Urano et al., 2000](#)). Under ER stress, ATF6 translocates to the Golgi apparatus where it is cleaved by proteases, releasing a cytosolic fragment that translocates to the nucleus and operates as a UPR transcription factor ([Ron and Walter, 2007](#)). Soluble ATF6 also can form heterodimers with XBP1 to induce the expression of specific genes ([Shoulders et al., 2013](#)).

Activation of PERK leads to the direct phosphorylation of the ubiquitous eukaryotic translation initiation factor 2 α (eIF2 α) to rapidly attenuate translation and reduce the ER lumen protein overload. This mechanism also induces the translation of ATF4, a transcription factor that controls the expression of genes involved in apoptosis, autophagy, amino acid metabolism, and antioxidant responses ([Walter and Ron, 2011](#)). In summary, the UPR integrates information about the intensity and duration of the stress stimuli, coordinating several critical responses to buffer fluctuations in protein folding, a process often altered in neurodegenerative diseases such as AD and PrDs.

2. Protein aggregation in AD and PrD

Although PMDs are characterized by the deposition of aggregates that consist of different proteins – amyloid-beta (A β) and tau proteins in AD and misfolded prion protein (PrP^{Sc}) in PrDs – several shared morphological, biological, and biochemical features have been described. The misfolded proteins in both diseases often contain stacks of β -sheets organized in a polymeric arrangement ([Soto et al., 2006](#)). Moreover, the typical molecular arrangement of these aggregates consists of clusters of misfolded proteins organized into cross- β structures, which can form patterns of deposition known as amyloid fibrils or diffuse/dense plaque-like deposits ([Blake et al.,](#)

[1996](#); [Parchi et al., 1999](#); [Soto, 2003](#)). These particular structural dispositions confer several adverse properties, such as proteotoxicity and disrupted protein clearance mechanisms. Additionally, because β -sheets can be stabilized by intermolecular interactions, misfolded proteins have a high tendency to form oligomers and larger polymers, which facilitates the accumulation of inclusions.

The main risk factor for developing most amyloid-related disease is aging ([Cuanalo-Contreras et al., 2013](#); [Finkel, 2005](#)), which suggests that older tissues and cells are more prone to form and accumulate misfolded protein aggregates. In fact, a global reduction in the buffer capacity of the protein homeostasis network is observed during aging in model organisms ([Douglas and Dillin, 2010](#)). However, it is unknown whether the age-dependent accumulation of insoluble proteins is a cause of cellular dysfunction resulting in aging or a consequence of the progressive decline of proteostasis. Overall, during the last two decades, a large body of histopathological, genetic, and biochemical studies have provided accumulating evidence that favors a critical role for protein misfolding and aggregation in AD and PrDs. The generation of transgenic animal models for rare genetic variants observed in familial cases of AD and PrDs have validated the involvement of protein misfolding and aggregation in these diseases ([Price et al., 1998](#)). However, the exact molecular mechanisms driving neuronal dysfunction in PMDs remains poorly understood.

Mutations in three genes have been linked to the development of rare familial and early onset forms of AD ([Bertram and Tanzi, 2008](#)). These genes encode for APP and presenilin (PSEN) 1 and 2. The mechanisms explaining the overproduction of A β peptide in familial AD (FAD) cases are starting to be elucidated, but little is known about the etiology of the most common sporadic forms of the disease (SAD). Given that FAD and SAD cases share several common clinical and histopathological characteristics, it is likely they also share common pathological mechanisms. Gradual changes in the steady-state levels of A β peptide in the brain are thought to initiate the amyloid cascade ([Karran et al., 2011](#); [Selkoe, 2004](#)). In AD and PrDs local accumulation of soluble oligomers and fibrils are thought to operate as a central initiator of neuronal dysfunction and in the long term cell death ([Walsh and Selkoe, 2004](#)). A β and PrP oligomers and fibrils associate with synapses and alter their function; they also can impair calcium homeostasis, and trigger detrimental processes, such as excitotoxicity, oxidative stress, ER stress and local inflammation ([Cornejo and Hetz, 2013](#); [Halliday and Mallucci, 2014](#); [Hetz and Soto, 2006](#); [Karran et al., 2011](#); [Selkoe, 2001](#)). In summary, protein misfolding and aggregation are common features of AD and PrD that may also result in the engagement of similar degenerative pathways, were we highlight the ability to self-propagate abnormal conformations and the irreversible perturbations to the ER protein homeostasis.

3. Protein misfolding amplification and transmissibility

Several groups have shown that the infectious properties of misfolded prion aggregates follow a kinetic profile, which is known as the nucleation-dependent mechanism ([Come et al., 1993](#)). This process involves two different phases, where the first stage or “lag phase” involves the slow formation of the initial stable misfolded aggregates. Here, small oligomeric structures referred to as “seeds” are formed through unfavorable intermolecular interactions between monomers. In the lag phase, the build-up of multimeric structures is slow and corresponds to the rate-limiting step leading to further aggregation. Subsequently, in the second stage or “elongation phase” the recruitment of new units to the growing aggregates takes place in an accelerated fashion until a plateau level of polymerization is observed. This seeding–nucleation process can be accelerated by the addition

of previously formed seeds, which provide a suitable surface for the incorporation of soluble components, promoting rapid fibrillar growth (Jarrett and Lansbury, 1993; Soto et al., 2006). This important molecular feature of amyloids led to the development of “Protein Misfolding Cyclic Amplification” (PMCA), a method for amplifying and detecting specific small amounts of misfolded oligomers present in tissues and biological fluids (Saborio et al., 2001). This technology, initially applied to the pre-symptomatic detection of prions (Soto et al., 2005), has been recently used to detect misfolded A β oligomers in cerebrospinal fluid (CSF), providing the basis for developing a highly sensitive test for AD diagnosis (Salvadores et al., 2014).

Prions are characterized by unique transmissible features, whereby misfolded forms of the prion protein catalyze the misfolding of neighboring normal prion protein, effectively turning normal prion protein into an infectious agent (Aguzzi et al., 2008; Castilla et al., 2005; Collinge, 2001; Prusiner, 1998; Salvadores et al., 2014). Interestingly, *in vitro* and *in vivo* studies have also shown that A β can be transmitted experimentally in animals through a prion-like mechanism (Eisele et al., 2010; Kane et al., 2000; Langer et al., 2011; Morales et al., 2011; Walker et al., 2002). Furthermore, A β amyloidogenesis can be accelerated *in vivo* after intracerebral inoculation of AD brain extracts into APP transgenic mice, which demonstrates both spread and transmission of neuropathological AD properties (Kane et al., 2000; Meyer-Luehmann et al., 2006; Watts et al., 2014). Similarly, Tau aggregation was recently reported to propagate through a Prion-like mechanism (de Calignon et al., 2012; Sanders et al., 2014). Even more surprisingly, the serial propagation of distinct strains of A β in susceptible transgenic mice was demonstrated using brain homogenates from AD patients, exhibiting differential morphology of A β deposition (Watts et al., 2014). This ability to replicate distinct strains, previously described in PrD (Colby and Prusiner, 2011), is associated with amplification of different conformations and quaternary assemblies of protein aggregates that affect different brain areas, which may help explaining the clinical and pathological heterogeneity observed in AD and CJD patients. Many other studies have also validated the concept of Prion-like propagation in other neurodegenerative diseases (Soto, 2012). However, we would like to reinforce the fact that AD has not been shown to be infectious.

4. Alteration of the secretory pathway and UPR activation

The contribution of the UPR to neurodegeneration is highly complex and difficult to predict based on the dual role of the pathway in cell survival and death, and the fact that distinct UPR signaling branches have specific impacts on the cell depending on the process affected. Genetic evidence in various models of PMDs indicate that depending on the disease context, specific UPR signaling branches may have distinct and even opposite effects on disease progression (reviewed in Hetz and Mollereau, 2014). For both AD and PrD, correlative studies in human post-mortem tissues have revealed the presence of ER stress markers in the brain; however, the impact of the UPR to the disease process is just starting to be elucidated. In PrD, several reports have shown that PrP misfolding induces ER stress and triggers the UPR in infectious and sporadic cases (Brown et al., 2005; Hetz et al., 2003, 2005, 2008; Moreno et al., 2012; Rane et al., 2008; Steele et al., 2007; Torres et al., 2010; Xu and Zhu, 2012; Yoo et al., 2002); however, the activation of the UPR in familial PrD models is less clear (Quaglio et al., 2011). An initial hypothesis suggested that chronic ER stress contributed to neuronal loss by activation of a pro-apoptotic stress signal (Hetz et al., 2003); however, the genetic targeting of XBP1 or caspase 12 (an ER-resident caspase) in mice did not affect the progression or pathophysiology of the disease in a model of infectious prion (Hetz et al., 2008; Steele

et al., 2007). In contrast, two recent reports demonstrated that ER stress indeed has an essential role in triggering the cognitive dysfunction observed in infectious forms of PrDs. Sustained activation of PERK by prion replication was shown to trigger a strong translational repression of synaptic proteins that are synthesized through the ER-Golgi secretory pathway (Moreno et al., 2012). Reversion of this specific molecular defect fully reverted the behavioral and histological manifestation of the diseases (Moreno et al., 2012, 2013). Moreover, salubrial, an inhibitor of eIF2 α -P phosphatase complex (Boyce et al., 2005), significantly accelerated the disease in animals infected with prion (Moreno et al., 2012). These results suggested that this specific defect in the proteostasis network is responsible for generating key pathological features, which could be reverted by genetically manipulating the UPR (Moreno et al., 2012, 2013).

In AD patient-derived brain tissue, the presence of PERK and phosphorylated eIF2 α , XBP1 mRNA splicing, or increased levels of ER chaperones Bip/Grp78, Grp94 and PDI, strongly suggests the occurrence of ER stress in humans (reviewed in Cornejo and Hetz, 2013). Recent studies have delineated the individual effects of distinct UPR components on the progression of AD in animal models. For example, the expression of an active form of XBP1 in *Drosophila melanogaster* appears to protect against amyloid- β toxicity, potentially by preventing the accumulation of free calcium in the cytosol (Casas-Tinto et al., 2011). Similar results were reported in an over-expression model of Tau in transgenic flies (Loewen and Feany, 2010). In another *in vivo* model, the deletion of *Xbp1* in *C. elegans* also protected against amyloid- β and this effect correlated with enhanced autophagy levels (Safra et al., 2013), which is in line with what we described in mouse models of ALS (Hetz et al., 2009) and Huntington's disease (Vidal et al., 2012).

Importantly, a polymorphism in the *XBP1* promoter previously linked to bipolar disorders and schizophrenia in Japan (Kakiuchi et al., 2003) was recently proposed as a risk factor for developing AD in the Chinese population (Liu et al., 2013). Unexpectedly, analysis of the regulatory network controlled by XBP1s revealed that this transcription factor regulates the expression of a cluster of AD-related genes, including components of the γ -secretase complex, cyclin-dependent kinase 5 (CDK5), and other components of APP maturation and trafficking (Acosta-Alvear et al., 2007). In a different study, it was also demonstrated that PERK-eIF2 α signaling promotes APP processing and amyloidogenesis *via* direct regulation of β -secretase 1 (BACE1), where the inhibitor of phosphatase salubrial, directly increased the BACE1 levels and elevated A β production in primary neurons *via* eIF2 α (O'Connor et al., 2008). These findings suggested the existence of a positive feedback loop that under conditions of chronic stress may have deleterious consequences. In the same line, another study indicated that in AD models ER stress triggers JNK3 activation that could in turn increase the internalization and processing of APP, resulting in greater A β production and exacerbation of ER stress. This study proposed a “vicious cycle” that amplifies the ER-stress response and AD pathology (Yoon et al., 2012). We proposed a similar “stress cycle” for PrP misfolding in models of infectious PrD forms in which ER stress facilitates prion replication by inducing a partial misfolding of PrP^C (Hetz et al., 2007). As reported for AD genes, ER stress has also been shown to induce the gene expression of PrP (Dery et al., 2013).

Perturbations of ER calcium homeostasis may be a crucial event that triggers protein folding alterations in this organelle as reported in cellular models of AD and PrDs. Synthetic PrP-derived peptides, A β peptide, expression of PrP mutants, or the incubation of cells with infectious forms of PrP alters calcium homeostasis in the ER (Ferreiro et al., 2006, 2008a,b; Hetz et al., 2003; Torres et al., 2010). A close correlation has been reported between alterations of ER calcium homeostasis and the occurrence of ER stress-mediated apoptosis in models of PrDs (Hetz and Soto, 2006) and AD (Bezprozvanny and Mattson, 2008). Importantly, an

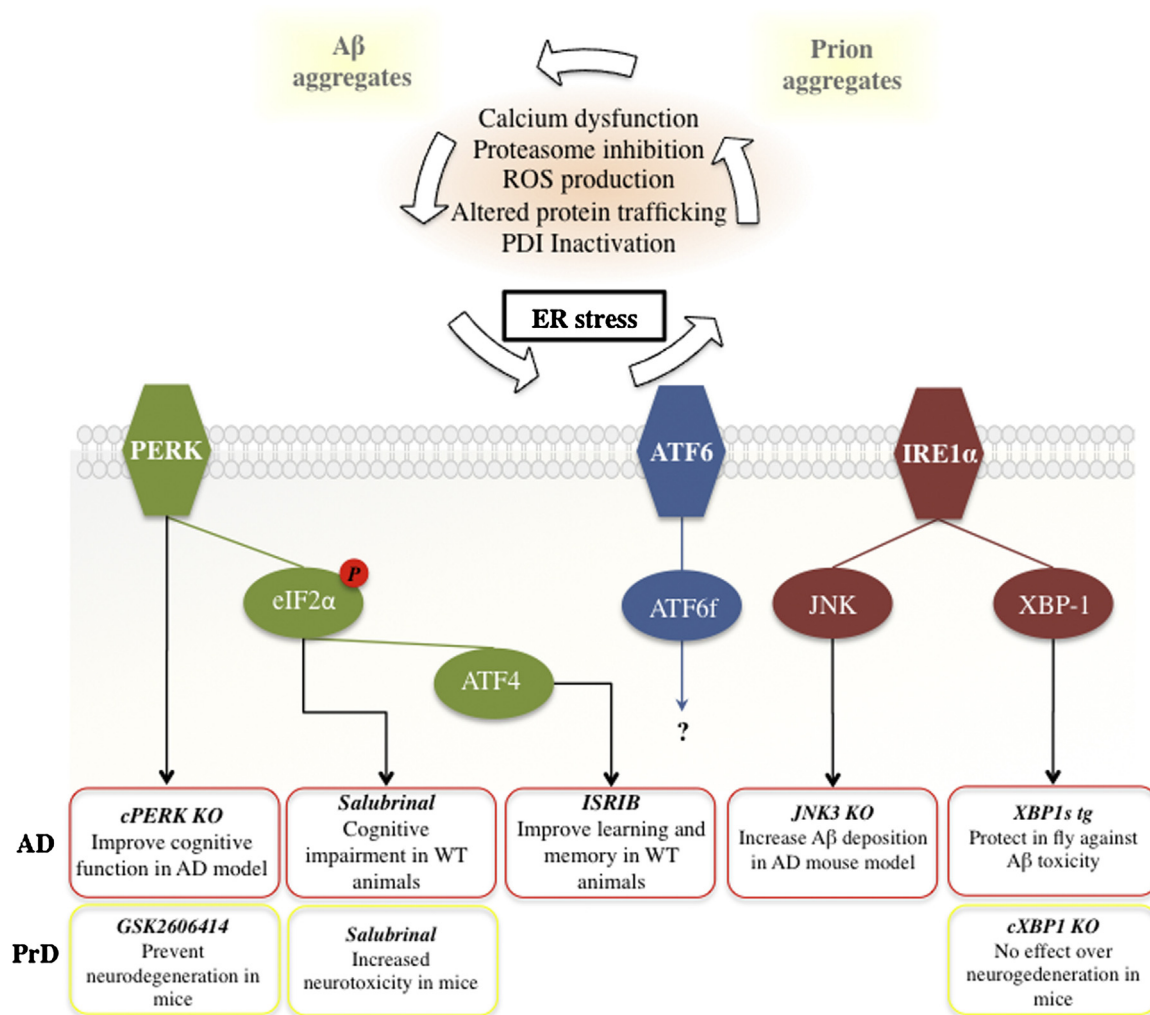


Fig. 1. The impact of UPR signaling on AD and PrD progression. Several perturbations of ER homeostasis generated by Aβ and prion aggregates favor Ab and PrP amyloid formation, a process characterized as a “vicious cycle” of aggregation. Manipulation of PERK by conditional CNS knock-out animals (cPERK KO) or treatments with PERK inhibitors improves cognitive functions and reduces neurodegeneration in both diseases. Salubrinal treatment, which promotes sustained eIF2α phosphorylation, produces deleterious effects in the progression in both AD and PrD. ISRIB treatment, which inhibits eIF2α phosphorylation, improves cognitive memory in WT animals. JNK3 knockout increases cortical Aβ aggregation in an AD mouse model. For XBP1, overexpression of the active factor (XBP1s tg) protects against Aβ toxicity in a fly model of AD; knock-out of this factor does not appear to affect neurodegeneration in PrD.

inhibitor of calcineurin (a calcium-dependent protein phosphatase) can reduce levels of neurodegeneration caused by the spread of PrP^{Sc} in an animal model (Mukherjee et al., 2010). Together these results suggest that alteration of ER homeostasis is a common factor involved in PrD and AD pathogenesis, and may be triggered secondarily to ER calcium disruption.

5. Targeting the UPR to improve cognitive impairment

The UPR is becoming an attractive target for drug discovery given the identification of small molecules that specifically inhibit selective components with proven efficacy in preclinical models of disease (Hetz et al., 2013; Maly and Papa, 2014), including neurodegenerative conditions (Hetz and Mollereau, 2014). Several pharmaceutical companies and academic laboratories are developing high-throughput screening methods to identify molecules that selectively modulate distinct UPR signaling modules. In addition, gene therapy using RNA interference technology or recombinant viral vectors is emerging as an attractive approach to selectively modulate UPR function in the central nervous system (reviewed in Hetz et al., 2013).

Regulation of protein synthesis have been known for decades to be essential for the process of learning and memory (Costa-Mattioli et al., 2009). For example, studies in mouse models have revealed that eIF2α phosphorylation and ATF4 expression have a physiological role in the nervous system in cognitive aspects of the brain. Under stress conditions, inhibition of protein synthesis through eIF2α operates as a survival pathway, referred to as the “integrated stress response” that involves several kinases, including PERK. Exacerbated phosphorylation of eIF2α produces cognitive impairment, specifically by inhibiting long-term potentiation and memory consolidation (see examples in Costa-Mattioli et al., 2005, 2007; Jiang et al., 2010; Ma et al., 2013; Sidrauski et al., 2013).

A recent study in AD models indicated that the genetic deletion of two eIF2α kinases, PERK and General control non-derepressible-2 (GCN2), strongly prevented phosphorylation of eIF2α and reduced the deficits in synaptic plasticity and spatial memory (Ma et al., 2013). In addition, pharmacological inhibition and genetic deletion of another eIF2α kinase, termed dsRNA-dependent protein kinase (PKR), showed enhanced basal levels of memory processes (Zhu et al., 2011). These findings support eIF2α kinases as potential therapeutic targets for improving memory consolidation and synaptic dysfunction in AD. As mentioned, the activation of the

PERK/eIF2 α UPR pathway in PrD models also led to a reduction in the expression of synaptic proteins and cognitive and motor impairment (Moreno et al., 2012). The same study revealed that overexpression of the eIF2 α phosphatase GADD34 reduced eIF2 α -P levels and restored synaptic protein levels, synaptic transmission, and synapse number in the CA1 hippocampal region. In addition, the overexpression of GADD34 had a significant effect on expanding the life-span of prion-infected animals (Moreno et al., 2012).

Genetic manipulations are often successful in model systems, however, several barriers still impede the translation of these genetic therapies to humans (Pauwels et al., 2009), which has made small molecule inhibitors a strong alternative. Chemical probes for inhibiting PERK pathways are in active development for their use as anti-tumor agents. A drug screening identified GSK2606414 as an orally available and selective inhibitor of PERK (Axten et al., 2012). Remarkably, a recent study indicated that GSK2606414 crossed the blood–brain barrier through oral administration and abrogated the clinical and pathological characteristics associated with accumulation of misfolded prion in a PrD mouse model; however, despite the neuroprotective effects, GSK2606414-treated animals suffered from body weight loss and mild hyperglycemia (Moreno et al., 2013), likely due to systemic effects of PERK inhibition in pancreatic function (Zhang et al., 2002). Another interesting drug screening identified a small molecule termed ISRIB as a potent inhibitor of the downstream consequences of eIF2 α phosphorylation, including ATF4 expression (Sidrauski et al., 2013). ISRIB also crosses the blood–brain barrier, has favorable pharmacokinetics, and showed no overall toxicity in mice. ISRIB-treated mice display significant enhancement in spatial and fear-associated learning (Sidrauski et al., 2013) consistent with the negative role of ATF4 in the process. So far there have been no studies of ISRIB in neurodegenerative disease models.

Altogether, these findings support the concept that deregulation of the PERK/eIF2 α pathway and abnormal translational repression could be involved in the cognitive impairment reported in AD and PrDs, placing ER stress as a central and common pathogenic denominator. Thus, targeting PERK/eIF2 α may represent a novel opportunity to reduce cognitive impairment observed in PMDs. However, comparative and systematic studies are needed to better define the true therapeutic value of manipulating ER stress levels and to identify possible side effects of the available drugs (e.g. GSK2606414 and ISRIB). Understanding these side effects at the system level remains an important subject for drug validation in preparation for future clinical trials (Hetz et al., 2013).

6. Concluding remarks

With an aging global population, the number of patients with neurodegenerative diseases is increasing dramatically. To date, there is no cure or effective treatment for PMDs; as such, the social and economic burdens are increasing rapidly. As highlighted here, we propose that the identification of common pathways that are active across a large spectrum of disorders could be a promising target for new therapeutic agents, especially for infrequent diseases with lower pharmaceutical interest.

In this article, we have compared the most recent evidence supporting a connection between AD and PrD at the level of pathogenic mechanisms, focusing on ER stress as a converging event in both diseases (Fig. 1). Chronic ER stress emerges as a key factor driving neuronal degeneration and cognitive impairment beyond cell death, a late event on disease progression. Moreover, ER stress may play a relevant role in prion and amyloid generation and spreading of the pathology in the brain possibly through a “vicious cycle” that interrelates protein aggregation, ER stress, and neurodegeneration. As discussed here, recent discoveries in the field

have revealed that manipulation of the UPR can have positive effects that attenuate neurodegeneration and improve cognitive alterations. Taken together, the selected evidence described here suggests that UPR manipulation represents a transversal target for treating several PMDs. To maximize the effectiveness of genetic and pharmacological therapies, however, the specific consequences of UPR manipulation need to be defined in more detail. Systematic studies are needed to elucidate the effects of targeting the specific stress pathways in order to reveal the exact contribution of the UPR to neurodegeneration and define its full potential as a therapeutic target.

Acknowledgements

We apologize to all colleagues whose work could not be cited owing to space limitations. This work was funded by FONDECYT 1140549, Millennium Institute No. P09-015-F, Ring Initiative ACT1109, FONDEF grant No. D1111007, grant USA2013-0003, ECOS-CONICYT13502, The Michael J Fox Foundation for Parkinson Research, ALS Therapy Alliance, Muscular Dystrophy Association, Alzheimer’s Disease Association, The Frick Foundation, and Foundation COPEC-UC (CH), FONDECYT 3140466 (CDA), and CONICYT PhD fellowship (V.H.C.).

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