1 Introduction

Prion diseases are a collection of conditions traditionally described as being caused by abnormal folding of cellular prion protein, resulting in a development of an abnormal form which is protease resistant. Due to the complexity of the nomenclature regarding prion proteins (the use of PrPsc to refer to all transmissible prions vs. scrapie, PrPprotease resistant vs. PrPsen, the use of prion to refer to all prion protein vs. abnormal protein, etc.), the authors will refer to any disease specific conformation as PrP TSE and the normal, cellular form as PrP c as suggested by Brown and Cervenakova [1].

Prion diseases are found throughout the animal kingdom, including in humans, and can be generated sporadically, brought about by random mutations; genetically, transmitted as autosomal dominant traits and invariably cosegregate with mutations in Prnp; and via infection, either by ingesting infected neural tissues or by accidental exposure during a medical procedure [2]. While the most common form of the disease found in humans is the sporadic Creutzfeldt - Jakob disease (CJD), other forms of prion diseases have been identified: such as variant CJD and Kuru, acquired forms of the disease, and Fatal Familial Insomnia and Gerstmann-Sträussler-Scheinker disease, genetic diseases caused by mutations in the gene Prnp. While these diseases are rare in the population, they are devastating to those that are effected and are caused by abnormal prion proteins accumulating in the nervous system where they cause neurodegeneration, and ultimately, death.

1.1 Conversion of PrP c to PrP TSE

Like many proteins, PrP c, a GPI linked protein, is processed in the ER and trafficked to the Golgi apparatus, where it is then shuttled to the plasma membrane [3]. PrP c is then internalized and trafficked to the early endosome; here it is sorted and returned to the plasma membrane by way of recycling endosomal carriers or delivered to...
the multivesicular body/late endosome and degraded by lysosomes [4]. The site of prion conversion from the PrP\(^c\) form, α-helix dominant, to the abnormal, protease resistant form PrP\(^{TSE}\), β-pleated sheet dominant, is not fully understood (Figure 1). There is evidence that prion conversion can occur in lipid rafts [5-7], at the surface of the cell [8-10], and in the endocytic pathway [11-13]. Interestingly, lipid rafts have been implicated in the mechanism of PrP\(^c\) internalization [14], leading one to ask if lipid rafts play a role in PrP\(^{TSE}\) endosome conversion. Moreover, retrograde transport towards the ER results in increased PrP\(^c\) to PrP\(^{TSE}\) conversion [15]. Adding to the difficulty of determining where prion conversion occurs is the fact that upon conversion a full length (FL) prion protein is generated that can be cleaved into a fragment known as C2 and varying amounts of FL PrP\(^{TSE}\) and C2 can be found depending on tissue type [16].

The mechanism involved in prion conformational change is not fully understood, and two models have been suggested [17]. The template assistance model proposes that upon contact, PrP\(^{TSE}\) can interact with properly folded PrP\(^c\) and change them into the PrP\(^{TSE}\) form. However, this model requires a stable PrP\(^{TSE}\) molecule to be present, and to date there is no evidence of the existence of this molecule. The more widely accepted model, the nucleated polymerization model, starts with the formation of a nuclei and aggregates grow upon attachment of PrP. The cells ultimately die due to the protein aggregation, which causes ER stress, leading to apoptosis. While the systematic association between the accumulation and apoptosis is not fully understood, there is speculation that the endoplasmic reticulum (ER) stress pathway is involved in the induction.

### 1.2 ER stress and UPR

Many newly translated proteins are targeted to the ER; here they undergo protein folding and are targeted for trafficking to the Golgi apparatus and subsequently the plasma membrane. When large amounts of protein misfold, the ER becomes stressed and invokes the unfolded protein response (UPR) pathway. The UPR pathway attempts to stop protein synthesis in order to allow chaperones to refold the current misfolded protein, degrade terminally misfolded proteins via ubiquitination and proteasomal degradation, and attenuate protein translation [18] and (Figure 2). Furthermore, loss of ubiquitin mediated proteasomal degradation can induce ER stress and the UPR. If the UPR is unable to relieve the ER stress, the cell dies via apoptosis. ER stress and changes in ubiquitin-proteasome degradation are implicated in

![Figure 1](image.png)

*Figure 1:* Ribbon structure of PrP\(^c\) converting to PrP\(^{TSE}\). PrP is shown with the correct folding of α-helices (a), while PrP\(^{TSE}\) is shown with its altered version containing β-sheets (b).
neurodegenerative diseases, including prion diseases [19]. Understanding the pathways involved in prion protein related ER stress is critical for the advancement in prevention and treatment of prion diseases.

In this review we will incorporate and discuss information from various studies that have been exploring the link between prion diseases and ER stress, as well as potential treatments for prion diseases as they relate to ER stress and the involvement of the UPR.

2 A role for ER stress in prion diseases

2.1 ER stress and Prions

ER stress has been implicated in prion misfolding, trafficking, and conversion to PrP\textsuperscript{TSE}. Treatment of mouse neuroblastoma cells with proteasome inhibitors or Tunicamycin, a chemical that induces ER stress, results in aggregation of insoluble PrP [20]. Moreover, inducing ER stress in primary neuronal cells results in increased aggregation and misfolding of PrP\textsuperscript{c}, and conversion of PrP\textsuperscript{c} to PrP\textsuperscript{TSE} is elevated in neuronal cell lines treated with ER stress inducers [21]. ER stress is also associated with decreased trafficking of PrP and accumulation of PrP to the cytosol [19, 22]. Moreover, ER stress associated proteins are upregulated in patients effected with variant CJD, an acquired form of CJD, and sporadic CJD [23] and is found to be associated with prion infection in animal models [19, 24-26]. These studies lend credence to the theory that ER stress induces accumulation and conversion of PrP.

2.2 The role of PERK and eIF2\alpha

One distinct link between prion diseases and ER stress is the phosphorylation of Eukaryotic Initiation Factor 2 alpha subunit (eIF2\alpha) by PERK. The unfolded protein response evolved to deal with ER stress and is initiated by activating transcription factor 6 (ATF6), inositol-requiring kinase 1 (IRE1), and pancreatic ER eIF2\alpha kinase (PERK) [27]. These molecules are found bound by Grp78/BiP; Grp78/BiP binds to misfolded protein and sequesters it in the ER, resulting in activation of IRE1, ATF6, and PERK and downstream molecules as shown in Figure 2 and (ibid).

Activated IRE1 splices XBP1 mRNA leading to the production of sXBP1, which when translated, functions to enhance the transcription of genes involved in protein folding, secretion, and ER-associated degradation. ATF6 is transported to the Golgi apparatus where it is processed

Figure 2: ER stress mediated UPR pathways. The UPR is mediated by three ER-resident transmembrane proteins, IRE1, ATF6, and PERK. These proteins sense ER stress through Grp78/BiP binding/release to their luminal domains and/or through direct interaction with unfolded proteins. This leads to the activation of downstream mediators that help clear the backlog of misfolded proteins.
into its active form and then translocates to the nucleus and prompts expression of the ER associated proteins. PERK dimerizes and induces phosphorylation of eIF2α [28]. Phosphorylation of eIF2α leads to a block in the initiation of protein synthesis for most proteins and an overall decrease in the translation of proteins [28]. This reduction also increases specific mRNA translations that were previously suppressed by the different forms of eIF2α complex created by the exchange. One such translated mRNA is activating transcription factor 4 (ATF4) [29]. ATF4 then causes transcription of genes heavily involved in the UPR, including Grp78/BiP, IRE1, and C/EBP homologous protein (CHOP) [30-32].

PrPTSE infection has been implicated in increasing phosphorylation of eIF2α in mouse models. Studies done using cell lines and primary neuronal cells infected with homogenate from prion infected mice showed a significant increase in eIF2α phosphorylation [33]. The same was observed by Moreno, et al. when using PrPTSE infected mice [26]. Moreover, inhibition of PERK/eIF2α phosphorylation resulted in reduced neuronal loss and synaptic failure [25, 26].

While these data show infection correlates with eIF2α phosphorylation, this may be strain specific. Prion proteins can adopt different infectious forms, leading to different strains [34, 35]. It is well documented that prion strains possess phenotypic differences with regards to incubation times, distribution in the host, and pathology [34, 36, 37]. Unterberger, et al. show in an earlier study that phosphorylated PERK and eIF2α does not accumulate in CJD infected individuals; furthermore, they went on to investigate PERK expression in mice infected with various prion strains and found that mice infected with variant CJD were indistinguishable from controls, while sporadic CJD infect mice had low expression of phosphorylated PERK and this was increased significantly in those infected with the Rocky Mountain Laboratory strain (RML) [38]. Interestingly, Moreno, et al. used the RML strain for their studies [26].

2.3 The ER, other forms of PRP, and disease

While PrPTSE, an abnormal form of PrP that is infectious and converted from the normal cellular form PrP*, is believed to be the causative agent of transmissible spongiform encephalopathies, significant pathology has been found in the absence of accumulation of PrPTSE [39]. Indeed, transmission and infection of the disease has been found in the absence of PrPTSE [40, 41]. Moreover, Piccardo, et al. found variation in infectivity based on PrPTSE isoform, as well as differences in the correlation between aggregation and disease [42]. This raises questions into the role of PrPTSE as being the sole inducer of pathology. Prion protein has two transmembrane forms found in the ER: the cytosol transmembrane form (Ctm-PrP), which has the COOH-terminus in the ER lumen and the NH2-terminus in the cytosol where it is accessible to proteases, and the N-terminal transmembrane form (Ntm-PrP), which has the NH2-terminus in the ER lumen with the COOH-terminus in the cytosol where it is accessible to proteases. Ntm-PrP has been confirmed to have no toxic effects on cells, unlike the Ctm-PrP form. Ctm-PrP causes neurodegeneration and prion disease associated symptoms in mice [43]. Interestingly, accumulation of PrPTSE is associated with increased production of Ctm-PrP [44].

Ctm-PrP spans the membrane between residues 112 and 135, and mutations in this region have been reported to be associated with familial CJD [45]. The presence of Ctm-PrP triggers an increase in mRNA levels of ER stress related proteins CHOP, PERK, Grp78/BiP, and Grp58 and activates apoptosis. Upon activation of ER stress, the pre-emptive quality control pathway blocks translocation of proteins into the ER and instead targets them for degradation in the cytosol by the proteasome [46]. Ctm-PrP retained in the ER, where it is subjected to proteasomal degradation, may cause harm to neurons by activating the ER stress-induced signal pathways. Typically, the UPR results in the up-regulation of chaperone proteins, but the expression of transcription factors such as CHOP and the phosphorylation of eIF2α can lead to apoptosis of neural cells which could promote CJD. Additional evidence of normal, cellular PrP induction of disease was shown by Rane, et al. PrPTSE accumulation induces ER stress and promotes the quality control pathway, leading to reduced translocation of prion protein into the ER and recruitment to the cytosol. This in turn leads to increased PrP C degradation, and the sustained activation of the quality control pathway overtime results in mild neurodegeneration [19]. However, evidence also exists that cytosolic, non-translocated PrP does not cause disease [47]. It may be that non-translocated PrP and the quality control pathway play a minor role in disease manifestation.

2.4 Additional ER stress molecules and prion disease

Interestingly, while PERK-eIF2α has been directly implicated in prion replication, the role of ATF6 and IRE1α appears to be less defined. Overexpression of IRE1α lacking the RNase domain which cleaves downstream target X-box binding protein 1 (XBP1) or a dominant negative form of
XBPI that cannot be cleaved, promoted insoluble PrP-formation, while introduction of cleaved ATF6 (functions as a transcription factor that upregulates UPR genes) reduced insoluble PrP-formation [21]. Moreover, ER stress led to an increased rate of PrP- conversion to PrP\[\text{TSE}\] (ibid).

More recently, XBPI has been implicated in regulating prion protein expression in a breast cancer cell line [48]. These data imply a role for UPR, via ATF6 and IRE1α, in blocking PrP conversion. However, studies utilizing mice lacking XBPI in neuronal cells found no effects on prion replication or aggregation nor in animal survival [24]. The discrepancy may be in the fact that the studies that implicate XBPI in regulating PrP employ overexpression studies and cell lines.

ER chaperones are upregulated in a number of models of prion disease, indicating that the presence of ER stress and the activation of the UPR may play a role in disease. ERp57 is a thiol-disulfide oxidoreductase or simply an ER resident foldase that catalyzes disulfide bond formation of a subset of glycoproteins and represents a key component of the calnexin/calreticulin cycle, molecules that assist the folding of glycoproteins in the ER. ERp57 interacts with PrP\[\text{C}\] [49], and overexpression of ERp57 (also known as GRP58) appears to protect against PrP\[\text{TSE}\] induced toxicity [50], suggesting that chronic ER stress may be part of the mechanism mediating neuronal loss. Moreover, ERp57 is upregulated in the brain tissue of those with sporadic and variant CJD and in a scrapie mouse model [50, 51]. Steady state protein levels of PrP are directly dependent on ERp57 expression using gain-of and loss-of-function in vivo and in vitro experiments [51]. Interestingly, loss of ERp57 results in the activation of the UPR via PERK [52], and the PERK/elf2α pathway promotes prion disease [25, 26, 33]. There is potential for ERp57 being a therapeutic target to treat prion diseases and other protein misfolding disorders since ERp57 has been implicated in other neurological diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS) [53].

A number of other chaperones are upregulated in prion diseases; however, it is unknown if these molecules play a role in regulating prions or if they are upregulated in response to stress induced by disease. Further studies will have to elucidate their role if any.

### 3 Treatment efforts

We do not understand the mechanisms behind the development of prion diseases, making them difficult to treat. Most of the treatment options available today are centered on improving the life of those affected by these diseases. There are a number of research studies that have found potential treatments for prion diseases; however, most of these treatment options have not been tested on humans. Those that have been shown to work in humans come with other possible issues, e.g. one treatment may work effectively for one patient, but not for another. There are a number of treatments currently being studied that are deserving of review; however, in this review we will now focus on potential drug treatments for prion diseases that involve the ER stress response pathway and the ER.

#### 3.1 Targeting PERK-elf2α

Studies focusing on the PERK-elf2α pathway have had some promising results. In an effort to stop accumulation of phosphorylated elf2α, researchers have attempted to block PERK from functioning [25, 26]. Overexpression of the elf2α phosphatase, GADD34, results in reduced neurotoxicity [26], and treatment with an inhibitor of PERK halts prion disease in mice [25]. However, the UPR is crucial to the secretory system, and this approach leads to issues with regards to pancreas function [25]. Attempts have also been made to target molecules downstream of elf2α by using the small molecule N,N’-trans-(cyclohexane-1,4-diyil)-bis-(2-(4-chlorophenoyo) acetamide (ISRIB). ISRIB decreases the amount of ATF4, while leaving the level of phosphorylated elf2α intact and partially restores protein synthesis in mice neurons; however, this molecule is highly insoluble, making it unlikely to be used for this purpose in the human counterpart of the disease [54]. Future studies into modifying the current drug structure to make it soluble, yet maintain its function, are crucial for developing this drug for treatment in humans. Studies exploring molecular inhibitors of the PERK/elf2α pathway have implications beyond that of prion diseases. The role of this pathway in other neurodegenerative diseases is well documented [55].

#### 3.2 Targeting the Ubiquitin Proteasome System

The Ubiquitin Proteasome System (UPS) is involved in ER associated degradation (ERAD). Proteins that are unable to fold correctly are exported to the cytosol where they are ubiquitinated and degraded by the proteasome [56]. Accumulation of prion protein in the cytosol leads to neurodegeneration [19, 57]. Moreover, evidence exist that PrP\[\text{TSE}\] can bind to and inhibit the function of the 26S proteasome [58, 59]. Impairment of the UPS plays a
role in prion disease. Treatment of cells with proteasome inhibitors leads to accumulation and aggregation of PrPc and PrP TSE in the cytosol [60, 61]. Mutations in E3 ubiquitin ligase Hectd2 is linked to susceptibility to Kuru and variant CJD [62], and a null mutation in the gene encoding a putative E3 ubiquitin ligase, Mahogunin, causes a spongiform neurodegeneration [63]. Moreover, PrPc found in the cytosol when the proteasome is inhibited can convert into a PrP TSE-like molecule [64]. Using a mouse reporter system, Mckinnon, et al. show that UPS dysfunction occurs early upon prion infection and correlates with PrP TSE accumulation [65]. In addition, UPS impairment correlated with the accumulation of ubiquitinated substrates, and treatment of prion infected cells with a small molecule proteasome activator reduced polyubiquitinated substrates and the levels of PrP TSE. Experiments will have to be done in vivo to see if this small molecule proteasome activator is a viable candidate for prion disease therapy.

### 3.3 Targeting Autophagy

Autophagy is an ancient and conserved intracellular degradation system that allows cells to survive in times of stress or starvation by targeting cytosolic components to lysosomes. It also plays an important role in eliminating misfolded proteins, harmful substances, and defective organelles [66]. While low levels of autophagy occur in healthy cells, autophagy is upregulated by ER stress [67, 68, 69], and various studies indicate that autophagy plays a role in prion disease. Autophagic vacuoles were found in the synapses of the brain tissues of those affected with human transmissible spongiform encephalopathies [70]. Inducers of autophagy diminish accumulation of PrP TSE in cell culture models [71, 72]. Moreover, inducing autophagy in a mouse model of Gerstmann-Straussler-Scheinker disease using rapamycin inhibited accumulation of insoluble PrP and plaque formation in addition to delaying disease onset [73]. However, treatment resulted in apoptosis of glial cells, which is a concern for the development of long-term therapies. These results were supported by Ishibashi, et al. who also investigated if autophagy induced by rapamycin could promote degradation of PrP TSE in cells infected with a prion strain derived from an individual with GSS [74]. However, they found rapamycin had no effect on other prion strains, 22L and Chandler, again indicating the importance of taking in account strain and prion conformation in treatment.

A study using astemizole, a drug used to treat seasonal allergies in humans that crosses the blood brain barrier, showed the drug induced autophagy and increased survival times in PrP TSE mice infected with the RML strain [75]. Additionally, they showed that astemizole was effective in inhibiting the propagation of the 22L and RML prion strains in vitro. Astemizole is an attractive drug for further study due to our understanding of its effects in humans and its ability to target multiple prion strains.

### 3.4 FK506 in the regulation of calcineurin and Ca²⁺ flux

Introduction of PrP TSE or PrP mutants that cause hereditary Creutzfeldt-Jakob disease or Fatal Familial Insomnia into neuronal cells results in the release of calcium from the ER and activation of the UPR [23, 76]. This leads to increased upregulation of calcineurin [77], which is known to promote apoptosis [78]. Treatment of prion infected mice with calcineurin inhibitor FK506 diminishes clinical disease [77]. Furthermore, treatment of mouse neuroblastoma cells with FK506 results in loss of PrP TSE, and treatment of cells with FK506 blocks cellular PrP translocation to the ER and promotes degradation in a Ca⁺² independent manner [75, 79]. This is of importance because PrP TSE cannot be produced in the absence of PrP [79], and FK506 could be used to block progression early in disease. One difficulty to this strategy is that prion diseases are hard to diagnose early on, and therefore, use of the drug in this manner must be preceded by better detection methods. The study by Stocki, et al. also implicated FK binding protein 10 as a target for blocking prion disease, as results from knocking down this molecule mirrored those from FK506 treatment [79].

Interestingly, FK506 has also been implicated in reducing PrP TSE via activation of autophagy. Nakagaki, et al. found FK506 promoted PrP TSE clearance via activation of autophagy, while another study showed FK506 (also known as tacrolimus), reduced PrP TSE in a manner that was not dependent on autophagy. Of note, these two studies used different strains of prions and this could very well explain the discrepancy between results [75, 80]. Dysregulation of neuronal Ca²⁺ signaling, autophagy, and the UPR have been implicated in other disorders of the brain such as Alzheimer’s and schizophrenia [81-83]; moreover, they possess interacting pathways [84]. This implies that understanding how FK506 functions in blocking prion disease can have overarching effects.
3.5 Using Bile acids to inhibit prion disease

The bile acids tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA) have been shown to be neuroprotective in other protein misfolding disease models including Parkinson’s, Huntington’s and Alzheimer’s diseases, and also in humans with ALS [85]. Furthermore, TUDCA decreases phosphorylated eIF2α and is linked to regulation of the UPR pathway [86, 87]. TUDCA and its precursor UDCA reduced PrP conversion in cell culture and infected cerebellar slice culture models [88]. UDCA also prolonged survival in RML prion-infected mice, although these findings were limited to the males, implying the gender-specific difference in drug metabolism. TUDCA and UDCA could be therapeutic options for treating prion diseases for the following reasons: (a) they have effects on both prion conversion and neuroprotection, (b) they are natural compounds and are orally bioavailable, (c) they are permeable to the blood-brain barrier, and (d) they are FDA-approved for the use in humans.

4 Conclusion

We have illustrated in this review that the unfolded protein response and ER stress play an important role in prion diseases. Currently, there is no standard cure for prion diseases. Targeting the UPR and molecular pathways associated with ER stress that play a role in prion disease has the potential to allow us to develop therapies. Using the ER stress pathway interactions and correlations, we can better understand the routes available for treating prion disease.

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