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Protein folding stress in neurodegenerative diseases: a glimpse into the ER

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Several neurodegenerative diseases share common neuropathology, primarily featuring the presence in the brain of abnormal protein inclusions containing specific misfolded proteins. Recent evidence indicates that alteration in organelle function is a common pathological feature of protein misfolding disorders, highlighting perturbations in the homeostasis of the endoplasmic reticulum (ER). Signs of ER stress have been detected in most experimental models of neurological disorders and more recently in brain samples from human patients with neurodegenerative disease. To cope with ER stress, cells activate an integrated signaling response termed the unfolded protein response (UPR), which aims to reestablish homeostasis in part through regulation of genes involved in protein folding, quality control and degradation pathways. Here we discuss the particular mechanisms currently proposed to be involved in the generation of protein folding stress in different neurodegenerative conditions and speculate about possible therapeutic interventions.

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Introduction

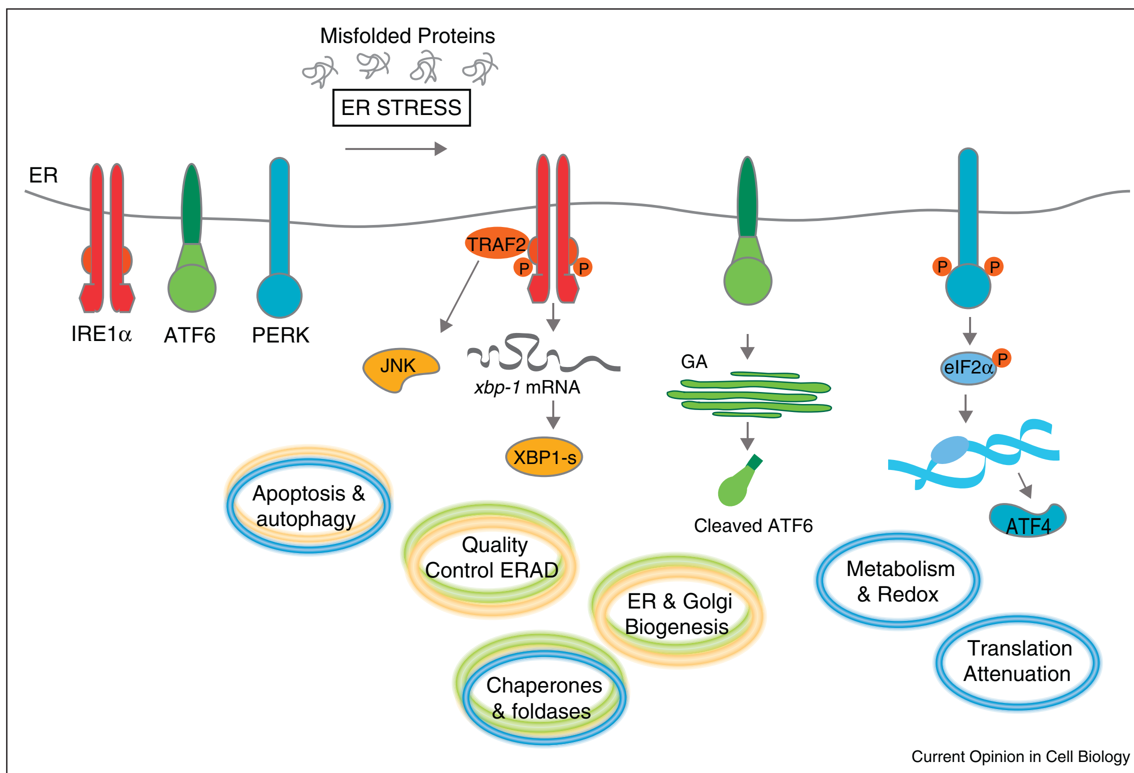
Most neurodegenerative disorders share a common neuropathology associated with the accumulation of abnormal protein aggregates or inclusions in the brain containing specific misfolded proteins. These diseases include Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Huntington's disease (HD), prion-related disorders (PrDs), and many others [1–4]. Abnormal protein aggregation in these diseases alters essential cellular functions, leading to neurological impairment and, in many cases neuronal loss. General perturbations to neuronal function could be related to synapse abnormalities, alteration in axonal transport, oxidative stress, proteasome inhibition, among other effects. Accumulating evidence in different neurodegenerative diseases indicates that subcellular organelle stress is a salient pathological event. Much attention has been given in the last ten years to the alterations of a particular subcellular organelle, the endoplasmic reticulum (ER), in the disease process. The ER is an essential compartment for the maturation and processing of proteins folded through the secretory pathway. In many neurodegenerative diseases the appearance of signs of ER stress is observed in the symptomatic and late disease stage. This article centers on recent findings illustrating the impact of protein folding stress at the ER in neurodegenerative conditions with distinct etiologies.

Cellular adaptation to protein folding stress: the UPR, ERAD and autophagy

One of the main functions of the ER is to initiate protein folding in the secretory pathway. A complex and dynamic network of protein chaperones, foldases, and co-factors are expressed at the ER lumen that catalyzes the folding and maturation of proteins, preventing their abnormal aggregation or misfolding. The ER also operates as a major calcium intracellular store and plays a vital role in the synthesis of lipids. Different alterations in ER homeostasis trigger the accumulation of abnormally folded proteins in the ER lumen, leading to a condition referred to as ER stress. ER stress engages the unfolded protein response (UPR), an adaptive signaling reaction that augments the cell's capacity to produce properly folded proteins and decreases the unfolded protein load [5]. Activation of the UPR affects the expression of different proteins with functions in almost every aspect of the secretory pathway, including folding, quality control, protein entry into the ER, ER-associated degradation (ERAD), autophagy-mediated degradation, and many other effects (Figure 1). The ERAD pathway is constituted by different components including chaperones, protein transporters, and ubiquitin-related enzymes that sense, deliver, and retrotranslocate misfolded proteins to the cytoplasm for proteasome mediated degradation [6].

There are three main types of ER resident transmembrane signaling proteins that operate as stress sensors that activate UPR signaling responses, These sensors include double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase (PERK), activating transcription factor 6 (ATF6), and inositol requiring kinase 1

Figure 1



The unfolded protein response (UPR). Accumulation of misfolded proteins at the ER lumen triggers an adaptive stress response known as the UPR mediated by three types of ER stress sensors: IRE1 α, PERK, and ATF6. In cells undergoing ER stress, IRE1α dimerizes and autophosphorylates, leading to the activation of its endoribonuclease activity at the cytosolic domain. Active IRE1α processes the mRNA encoding XBP1, which is a transcription factor that upregulates many essential UPR genes involved in folding, ERAD, organelle biogenesis, and protein quality control. In addition, active IRE1α activates alarm responses mediated by the JNK. Additionally, activation of PERK decreases the general protein synthesis rate through phosphorylation of the initiation factor eIF2α. eIF2α phosphorylation increases the translation of the ATF4 mRNA, which encodes a transcription factor that induces the expression of genes involved in amino acid metabolism, antioxidant responses, apoptosis, and autophagy. ATF6 is a type II ER transmembrane protein encoding a bZIP transcriptional factor on its cytosolic domain and localized at the ER in unstressed cells. Upon ER stress induction, ATF6 is processed at the golgi apparatus (GA) releasing its cytosolic domain, which then translocates to the nucleus where it increases the expression of some ER chaperones, ERAD-related genes, and proteins involved in ER and GA biogenesis.

(IRE1) (Figure 1). All these proteins transduce information about the protein folding status at the ER lumen to the nucleus and cytosol by controlling expression of specific transcription factors and other rapid effects on protein synthesis. IRE1α is a Serine/Threonine protein kinase and endoribonuclease that directly regulates through its ribonuclease domain the unconventional splicing of the mRNA encoding the transcription factor X-Box Binding protein-1 (XBP1). This mRNA processing event leads to the translation of a more stable protein, XBP1s [7–9]. XBP1s translocates to the nucleus and controls the induction of a subset of UPR-related genes that function in protein quality control, folding, the ERAD system, and ER and GA biogenesis [5] (Figure 1). The intensity and kinetics of IRE1α signaling are tightly regulated by the formation of a protein complex with many regulators, a scaffold termed the *UPRosome* [10,11] (reviewed in [12,13]). IRE1α has other functions in cell signaling, initiating the activation of alarm pathways mediated by Apoptosis Signal-regulating Kinase 1 (ASK1) and c-Jun-N terminal kinase (JNK) pathway [14–16], in addition to modulating macroautophagy levels, here referred to as autophagy [17]. Macroautophagy is a survival pathway classically linked to adaptation and survival against nutrient starvation. Conversely, in cells undergoing ER stress, autophagy may serve as a mechanism to eliminate abnormally aggregated proteins and damaged organelles [18].

Activated PERK phosphorylates the eukaryotic translation initiation factor 2α (eIF2α), inhibiting translation into the ER [19,20]. eIF2α phosphorylation augments the specific translation of the mRNA encoding activation of transcription-4 (ATF4), a transcription factor that controls the upregulation of a subset of UPR-target genes that function in redox homeostasis, amino acid metabolism, apoptosis, and autophagy [21–24,25•,26] (Figure 1). Finally, activation of ATF6 leads to its translocation from

the ER membrane to the Golgi apparatus where it is proteolytically processed, releasing the cytosolic domain which expresses a transcription factor that translocates to the nucleus and upregulates several ER chaperones, ERAD-related genes and XBP1 mRNA [27,28].

Prolonged ER stress leads to apoptosis where different regulators have been identified (reviewed in [5,29,30]), including members of the BCL-2 family of proteins [10,29,31–33]. Activation of ASK1 and JNK also regulates apoptosis under ER stress conditions [15,16]. Sustained PERK signaling is proposed as a pro-apoptotic effector [34] possibly through the induction of CHOP/GADD153 and the BCL-2 family member BIM and PUMA [19,35–37]. Many additional components of the ER stress apoptosis pathway have been identified (see specialized reviews in [31,33]).

A function of the UPR in the physiology of the nervous system?

ER stress is observed in many physiological processes in secretory cells such as plasma B lymphocytes, salivary glands and pancreatic beta cells. In all these tissues the UPR plays an essential role in maintaining survival and functionality of secretory cells (reviewed in [13,38,39]). The high demand for efficient protein folding and secretion in those cells constitutes an endogenous and physiological source of stress associated with the presence of large amounts of abnormally folded proteins that are generated during the normal protein synthesis and maturation process [6].

Although the impact of the UPR in maintaining the integrity of several secretory organs is known, its actual role to the physiology of the nervous system remains highly speculative. A possible role of XBP1 in the nervous system was proposed from genetic studies of human patients affected with bipolar disorders [40,41]. A polymorphism in the XBP1 promoter was identified as a risk factor for bipolar disorder and schizophrenia (see examples in [42–44]). Studies in *Xenopus* embryos demonstrated that XBP1 is a negative regulator of neuronal tissue differentiation during early brain morphogenesis [45]. Interestingly XBP1 expression is induced during neuronal development in *Caenorhabditis elegans* and its function regulates the assembly and transport of the glutamate receptor to the plasma membrane [46], an essential event for synaptic activity.

A role for XBP1 as a downstream signaling component of brain-derived neurotrophic factor (BDNF) was linked to neurite outgrowth [47]. Another report described activated UPR components in neurites [48]. Gene expression profile analysis from *xbp1* deficient primary neurons revealed that XBP1s controls the induction of GABAergic markers by BDNF signaling [49] perhaps explaining the neurite extension defects described in XBP1 knockout neurons. Translational control is essential for synaptic plasticity and learning and memory [50]. Interestingly, genetic evidence suggests that targeting ATF4 or eIF2α phosphorylation enhances memory acquisition, an effect mediated by GCN2 [51–53], an eIF2α kinase regulated by nutrient fluctuations (but not ER stress). Finally, a recent report indicated that chronic ER stress augments spontaneous excitatory neurotransmission in hippocampus cultured neurons [54]. It remains to be determined whether or not the UPR participates in cognitive functions of the nervous system.

ER stress in neurodegenerative conditions

Although signs of ER stress are observed in a variety of neurodegenerative diseases, the *in vivo* contribution of the pathway to the disease process has been established only in a few cases, and existing data are either correlative or arise from *in vitro* evidence. The functional significance of ER stress to neurodegeneration is complex and lends itself to three distinct but paradoxical interpretations. Activation of the UPR could promote neuronal protection by increasing the efficiency of protein folding and quality control, or it may represent a degenerative signal triggered by chronic disturbance of ER homeostasis. UPR activation may also represent a late and downstream event associated with extensive neuronal damage and cellular collapse not essential for the disease process (epiphenomena). In the following sections we discuss specific evidence linking ER stress to major neurodegenerative diseases.

Amyotrophic lateral sclerosis

ALS is the most common motoneuron neurodegenerative disease affecting adults, characterized by atrophy, muscle weakness and paralysis. ALS is associated with the selective degeneration of brain and spinal cord motoneurons [55,56]. Most ALS cases are referred to as sporadic (sALS), lacking a clear genetic component, whereas ten percent of the cases are familial (fALS). The primary mechanisms contributing to motoneuron degeneration observed in ALS remain controversial, and multiple alterations have been uncovered (see examples in [57–59]).

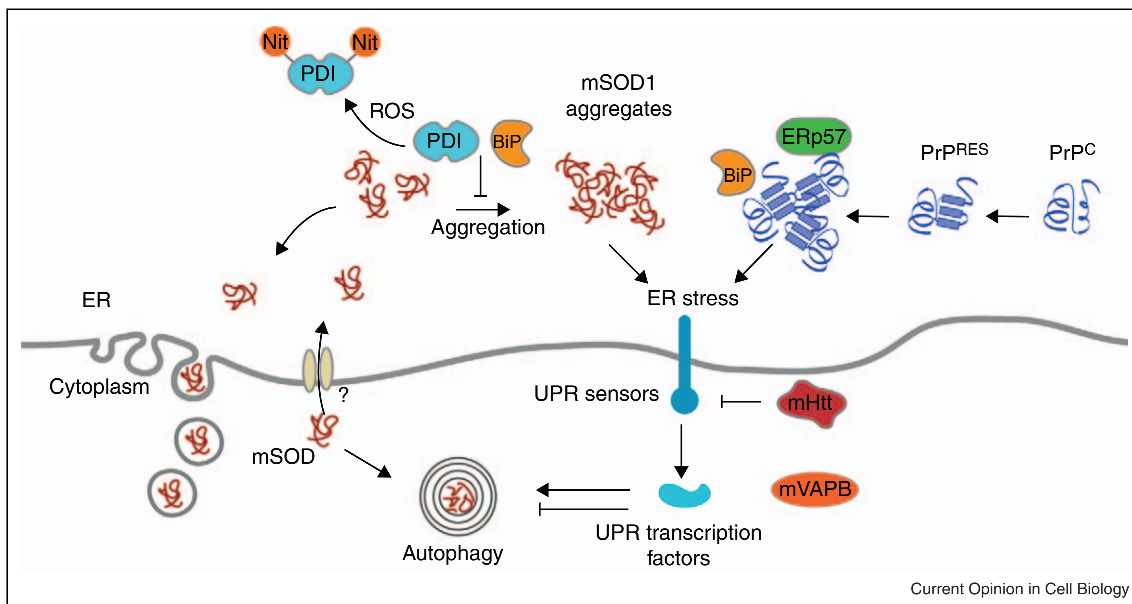
Accumulating evidence suggests that ER stress contributes to both sALS pathogenesis and fALS pathogenesis [60]. Increased levels of a variety of ER stress markers have been reported in spinal cord tissue of sALS patients [61,62••,63–65]. Approximately 20% of fALS cases are linked to more than 110 dominant mutations in the gene encoding superoxide dismutase-1 (SOD1). These mutations induce the misfolding and abnormal intracellular aggregation of SOD1, which is thought to contribute to the occurrence of neuronal dysfunction and death. Recent studies also suggest that Wild-type SOD1 aggregates and accumulates in sALS spinal cord [66]. Activation of the three major UPR signaling branches is observed in different mutant SOD1 transgenic mice [64,67–70,71•,72••,73,74]. A recent study

showed that only affected motoneurons of fALS mouse models are selectively prone to undergo ER stress, a pathological process observed from birth with activation before the detection of the earliest denervation [72••]. A proteomic analysis of spinal cord tissue from symptomatic SOD1^{G93A} transgenic mice identified ERp57 and PDI as the most highly induced proteins present. These two studies point to the occurrence of ER stress as a major cellular response activated in ALS models [67,72••].

A fraction of insoluble-high molecular weight species of mutant SOD1 accumulates inside the ER *in vivo* as demonstrated by many studies [67,69,75,76]. SOD1 possibly interacts with PDI or with BiP/GRP78 in ER enriched lysates [67,69] (Figure 2). The therapeutic effects of targeting the UPR were demonstrated after treatment of mutant SOD1 transgenic mice with salubrinal, a small molecule that induces eIF2α phosphorylation [77]. Salubrinal led to significant protection against disease progression, improved motoneuron survival, and extended life span [72••]. Similarly, another molecule that decreases ER stress levels, termed SUN N8075, also protects against experimental ALS [78]. We also recently investigated the possible contribution of ER stress to ALS using a genetic strategy [62••]. We knocked down components of the three UPR branches in a cellular model of fALS. As predicted reduced levels of ATF4 and ATF6 increased the rate of mutant SOD1 aggregation [62••]. In contrast, knocking down XBP1 unexpectedly reduced the generation of mutant SOD1 aggregates in cultured motoneurons. We also generated mutant SOD1 mice with a specific deficiency of *xbp1* in the nervous system [62••]. These mice exhibited delayed ALS disease onset and increased life span, uncovering an unexpected beneficial effect of targeting the IRE1α branch of the UPR [62••]. Both cellular and *in vivo* approaches in the context of XBP1 deficiency revealed an enhancement of mutant SOD1 degradation due to autophagy in motoneurons (Figure 2).

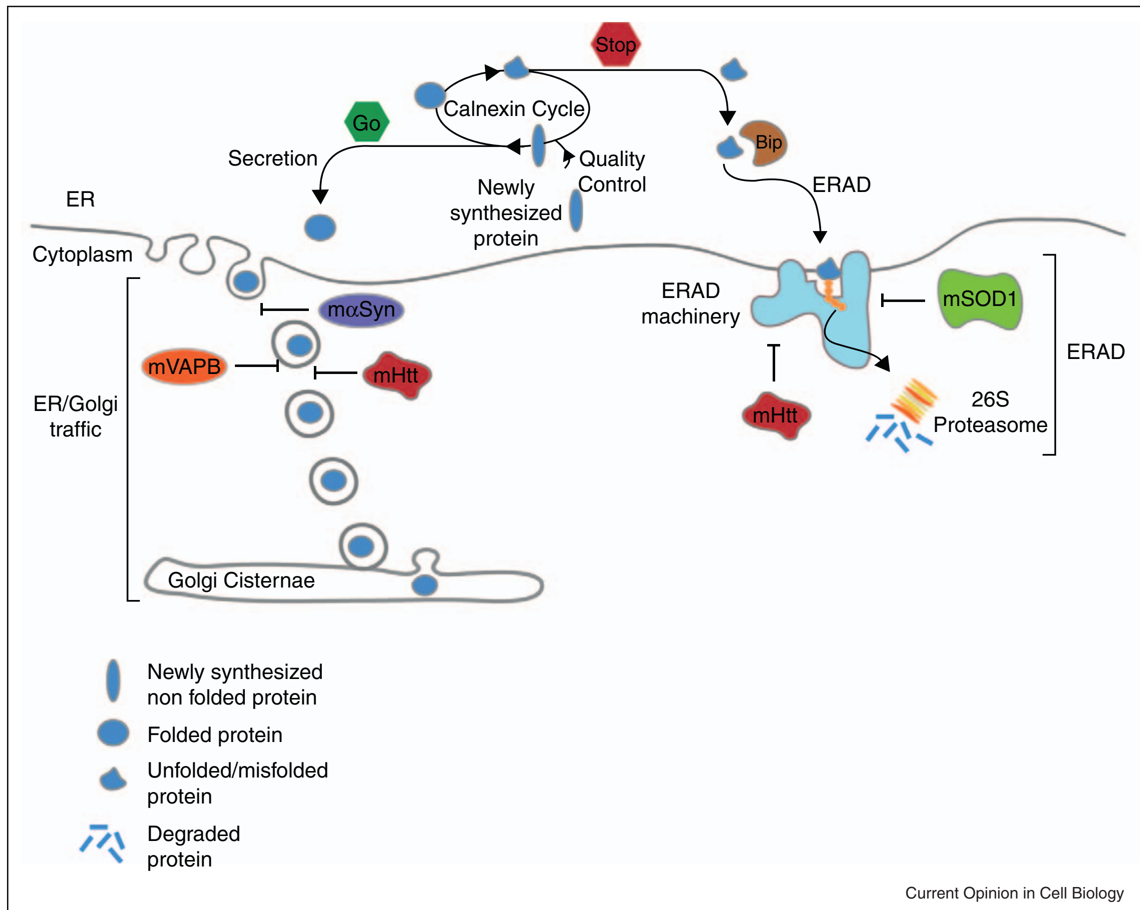
Several reports have uncovered possible causes of ER stress in ALS. For example, the cytosolic subpopulation of mutant SOD1 inhibits ERAD activity via decreased retro-translocation of ERAD substrates to the cytosol, inducing ER stress [71•] (Figure 3). Mutant VAPB causes fALS [79], through interacting with and inhibiting ATF6 and XBP1 [80–82] (Figure 3), increasing the vulnerability of motoneuron cells to ER stress-induced death [83]. Oxidative modifications of PDI, a key ER foldase, are also observed in sALS spinal cord tissue and in fALS mouse models [73]. PDI inactivation likely triggers a general perturbation of ER folding networks, possibly leading to chronic ER stress (Figure 2). Other factors may also contribute to the occurrence of ER stress in ALS,

Figure 2



Alterations in the function of ER chaperones and UPR-related components in neurodegenerative diseases. In many neurological diseases such as AD, PD and ALS, the oxidative modification of the active site of PDIs by nitrosylation leads to their enzymatic inactivation. This event may perturb the folding process at the ER, triggering ER stress. In addition, mutant SOD1 and PrP^{RES} accumulate and aggregate at the ER, which correlate with their stable interaction with ER chaperones such as BiP, PDI and ERp57/Grp58. This interaction may trap ER chaperones, altering protein folding networks with concomitant ER stress. In addition, expression of VAPB mutants (mVAPB) linked to fALS or mutant Htt (mHtt) alters the activity of UPR stress sensors and transcription factors. Accumulation of disease-related protein aggregates at the ER may directly or indirectly activate UPR stress sensors. UPR transcription factors control several cellular responses (Figure 1), including the positive and negative modulation of autophagy-mediated degradation of protein aggregates.

Figure 3



Alterations in ER-associated degradation (ERAD) and ER/Golgi trafficking triggers ER stress in some neurodegenerative diseases. Under normal conditions, newly synthesized proteins at the ER enter into the calnexin cycle for proper folding and quality control. If a protein becomes misfolded, it is targeted to the ERAD machinery for translocation to the cytosol and then degraded by the proteasome. Mutant Htt (mHtt) or mutant SOD1 (mSOD1) associated with fALS interacts with ERAD components, precluding the translocation of ERAD substrates from the ER to the cytosol, leading to the accumulation of abnormally folded proteins at the ER, generating ER stress. Properly folded proteins traffic from the ER to the Golgi for further maturation steps. Expression of mutant VAPB (mVAPB) associated with fALS and mHtt alter the trafficking between ER and Golgi. Similarly, mutant αSynuclein (mαSyn) blocks the exit of vesicles from the ER. Inhibition of vesicle transport between the ER-Golgi leads to the accumulation of cargo vesicles, triggering the accumulation of immature proteins at the ER, causing ER stress.

including alterations to axonal and dendritic trafficking of vesicles. For a detailed review see [60].

Accumulating evidence indicates that alterations in two proteins related to mRNA metabolism have an important role in ALS pathogenesis, including altered expression of TAR DNA-binding protein 43 (TDP-43) and Fused in sarcoma protein (FUS) (see review in [84]). For example, abnormal subcellular distribution and cytoplasmic aggregation of TDP-43 are widely reported in sALS and fALS cases, in addition to frontotemporal lobar degeneration [85]. Mice transgenic for a disease-linked mutant form of human TDP-43 develop progressive neurodegeneration associated with motoneuron loss, motor impairment, and accumulation of ubiquitin-positive aggregates [86]. Mutations in FUS are also genetically linked to fALS [87] and accumulation of FUS into protein inclusions is also observed in sALS cases [88]. Although protein misfolding and aggregation is associated with FUS and TDP-43-related neurodegeneration, it remains to be determined if ER stress is a relevant factor in their pathological effects.

Parkinson's disease

PD is the second most common neurodegenerative disease, and affects around 2% of individuals over 65 years of age [89]. PD is a slowly progressing neurodegenerative disorder affecting dopaminergic neuron viability in the *Substancia Nigra pars compacta* (SNpc). Most PD cases are sporadic but familial PD accounts for 2–3% of PD cases. One of the most studied PD-related genes is α-synuclein (αSyn) [90], which is observed in intracellular inclusions termed Lewy bodies.

Increasing evidence suggests that ER stress is a common pathological feature associated with several PD-linked genes and sporadic PD models. ER stress markers were reported in the *SNpc* of post-mortem tissue from sporadic PD human cases [91–93], and in another synucleinopathy (Multiple system atrophy) [94]. PDI inactivation occurs in PD brain through oxidative modification [95] (Figure 2). Cellular studies indicate that overexpression of mutant [96] and wild type [78] αSyn triggers chronic ER stress, inducing cell death. Reports in complementary model organisms demonstrated that the earliest defect following αSyn expression is a block in ER to Golgi vesicular trafficking [97,98]. Remarkably, the inhibition of ER-Golgi trafficking by αSyn expression triggers ER stress [97,98] possibly due to the accumulation of cargo vesicles, triggering the accumulation of immature proteins at the ER [12,99] (Figure 3). αSyn phosphorylation activates the UPR even before any detectable mitochondrial dysfunction is observed [100]. In addition, Parkin/PARK2 expression has a pro-survival activity against ER stress due to modulation of ERAD/proteasome pathway [101–103]. Expression of the Parkin substrate Pael-R triggers ER stress *in vivo* and *in vitro* [104–106], and manipulation of ER chaperone expression reverts the pathological effects of Pael-R [106]. Furthermore, loss of DJ-1/PARK7 triggers ER stress and proteasome inhibition [107]. Mutation in ATP13A2/PARK9 leads to its ER retention where it may exert neurotoxicity [108]. Finally, LRRK2/PARK8 deficiency in *C. elegans* triggers hypersensitivity to ER stress [109].

Remarkably, two gene expression profile analyses indicated that ER stress is a major cellular response in toxicological models resembling sporadic PD [110,111], and *chop* deficiency [112] or XBP1s overexpression [113] attenuated neurotoxin-mediated PD. Similarly, ATF6 deficient mice are more susceptible to neurotoxin-induced neurodegeneration at the *SNpc* [114]. At the mechanistic level, it was proposed that the generation of radical oxygen species by PD-triggering neurotoxins leads to the oxidation of proteins at the ER, possibly inducing protein misfolding and ER stress [115]. Taken together, these findings suggest that a common feature in sporadic and different genetic forms of PD is the occurrence of chronic ER stress.

Huntington's disease

Huntington's disease (HD) is a late-onset autosomal dominant neurodegenerative disease associated with progressive cognitive defects and motor abnormalities [116,117]. The disease results in a widespread neuronal dysfunction and selective neurodegeneration in the central nervous system, mostly affecting the striatum [116]. The expansion of a glutamine stretch within the N-terminal region of *huntingtin* (Htt) gene over ~40 repeats generates severe dominant neurotoxic properties [116–120].

UPR activation was noted in post-mortem HD brain samples [121]. Similarly, several studies in cellular models of HD suggest that ER stress may contribute to neurodegeneration [15,16,24,122•,123] (reviewed in [124]). Expression of SCAMP5 is markedly increased in human HD striatum and SCAMP5 down-regulation alleviates ER stress-induced by mutant Htt expression in cell culture [125]. At this time, only three studies are available describing the occurrence of ER stress *in vivo* in HD animal models [121,125,126]. The 18 amino-acid amino-terminus region of Htt generates an amphipathic alpha helical that can reversibly target to the ER and autophagosomes [127]. In addition, the association of Htt and membranes is dynamic because this interaction is modulated by ER stress [127], which may be a relevant factor for Htt aggregation [127].

Expression of mutant Htt leads to a pronounced defect in ERAD in yeast cells and mammalian models of HD, associated with an recruitment of essential ERAD proteins, triggering ER stress [122•,128] (Figure 3). Further, a recent report suggested that ATF6α processing is altered in animal models of HD and in patient HD samples [129]. However, most of these studies are correlative and no data on the function of ER stress/UPR signaling in the disease process *in vivo* are available. Genetic or pharmacological manipulation of the pathway is required to resolve this issue.

Prion-related disorders

PrDs are lethal neurodegenerative disorders whose hallmark is spongiform degeneration and accumulation in the brain of a protease-resistant and misfolded form of the cellular prion protein termed PrP^{RES} [130]. PrDs can be classified as sporadic, infectious, or autosomal dominant inherited forms, observed in both humans and other mammals. The most common PrD in humans is Creutzfeldt–Jacob disease (CJD) [130]. Upon synthesis, the normal cellular prion protein (PrP^{C}) is subjected to several post-translational processing events in the ER and Golgi before localizing to the plasma membrane in cholesterol-rich lipid rafts [131]. Most familial mutant PrP variants are retained and aggregated at the ER and Golgi [132]. In contrast, the generation of infectious PrP^{RES} is proposed to occur at the plasma membrane and during its cycling through the endocytic and lysosomal pathway [132]. The 'protein-only' hypothesis postulates that the pathogenesis of infectious PrD forms results from a conformational change of PrP^{C} to generate PrP^{RES}, possibly set off by a direct interaction between the two PrP forms [133].

Several groups have shown activated ER stress responses in PrD mouse models [134–139]. Similarly, cows affected with Bovine Spongiform Encephalopathy develop signs of ER stress in the brain [78]. Upregulation of Grp78/BiP, Grp94, and Grp58/ERp57 is observed In CJD brain

samples [136,140] and proteomic analysis of such brain samples demonstrated high expression of Grp58/ERp57 in cerebellum of human patients with sporadic CJD [140]. Grp58/ERp57 interacts with PrP and has neuroprotective effects *in vitro* against prion neurotoxicity [137] (Figure 2). In addition, scrapie infected neuroblastoma cells are more susceptible to cell death induced by the pharmacological activation of ER stress [136]. Further, expression of a familial PrP mutant triggers ER stress *in vitro* [141].

ER stress can trigger PrP^{C} misfolding and aggregation [142–144], and facilitates the conversion of PrP^{C} into PrP^{RES} in a cell free system [143]. Similarly, proteasome inhibition leads to the accumulation of a protease resistant form of PrP^{C} derived from the ERAD [145,146]. These observations may be relevant for understanding the occurrence of sporadic forms of CJD, the most common PrD in humans, where alteration in the folding/ quality control process or the ER environment may be a key event in initiating PrP misfolding. To evaluate the possible involvement of the UPR in PrDs we tested the susceptibility of a brain specific XBP1 conditional knockout mice to scrapie prion pathogenesis [135]. To our surprise, no effects were observed on the activation of ER stress responses, PrP^{RES} levels, neuronal loss or animal survival. Since the UPR in mammals is not limited to the IRE1/XBP1 pathway, activation of these alternative UPR pathways may well compensate for XBP1 deficiency in the prion model employed.

Alzheimer's disease

AD is the most common form of dementia of the elderly. AD is characterized by extracellular accumulation of fibrillar deposits of the amyloid-β peptide (Aβ) in senile plaques, intraneuronal neurofibrillary tangles consisting of abnormally hyperphosphorylated tau protein, in addition to oxidative stress, synaptic loss and neuronal degeneration [147]. A 4.5 kDa Aβ peptide is generated by successive proteolysis of the amyloid precursor protein (APP) by two proteases, beta-secretases and gamma-secretases. Mutations in the genes encoding APP or presenilin are associated with hereditary cases of AD and increased Aβ generation. Soluble oligomers of Aβ are highly neurotoxic, causing important deleterious effects on synaptic function and memory [148].

The exact mechanism involved in neuronal dysfunction in AD remains speculative. Recent studies from different laboratories implicate the participation of ER stress in the disease process. ER stress is observed in post-mortem brain samples from AD patients [149–155], in addition to PDI inactivation by oxidative inactivation [95]. Signs of ER stress have been observed in many cellular models of AD by independent groups [156–165]. Some AD-related proteins also alter ER stress signaling, including IRE1α and calcium homeostasis [148,166,167]. Some but not all *in vivo* studies have detected signs of ER stress in animal models of AD [166,168–170].

Other pathologies

Although little data are available about the impact of the UPR in other pathologies, emerging evidence indicates that ER stress may have a broader impact on disease conditions affecting the nervous system.

Lysosomal storage diseases

Lysosomal storage diseases are fatal neurodegenerative disorders that belong to a family of inborn metabolism errors. ER stress is observed in several models of lysosomal storage diseases including GM1-gangliosidosis [171,172] and Infantile Neuronal Ceroid Lipofuscinoses [173,174]. In contrast, no evidence of UPR activation was reported in models of other lysosomal storage disorders including Gaucher disease [175] and Niemann Pick type C [176].

Spinal cord injury

Spinal cord injury (SCI), a major cause of partial or complete loss of mobility can occur from mechanical trauma, ischemia, tumor invasion or developmental abnormalities. ER stress markers are observed in several models of SCI due to trauma (contusion and hemisection) and ischemia as an early event [177–180]. Treatment with a chemical chaperone decreases tissue damage in a SCI mouse model, associated with a reduction in the levels of ER stress [181]. However, all of the studies performed to date are correlative and the contribution of ER stress to SCI has never been addressed directly.

Myelin-related disorders

Myelinating cells including oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system produce large amounts of plasma membrane and proteins during the myelination process, that may render them particularly susceptible to secretory pathway function disruption (reviewed in [182]). ER stress markers are observed in models of various myelin-related disorders, including multiple sclerosis [183–188], Charcot-Marie-Tooth disease [189•], Pelizaeus-Merzbacher's disease [190], and Vanishing White Matter Disease [191,192].

Retinitis pigmentosa

Mutations within the rhodopsin gene lead to retinitis pigmentosa, an inherited form of retinal degeneration. Several rhodopsin mutants trigger ER stress *in vitro* and in animal models [193,194•,195,196]. Targeting *xbp1* in a *Drosophila melanogaster* model accelerates retinal degeneration [197]. Remarkably, subretinal delivery of a BiP expressing viral vector in a mutant rhodopsin transgenic rat led to reduction in ER stress levels, and improved neuronal survival and eye function [193]. Similarly, mutations in carbonic anhydrase IV, which is also linked

to retinitis pigmentosa, trigger chronic ER stress and apoptosis [198–200].

Concluding remarks

The exact role of the UPR in the central nervous system is not well defined. In this review we have summarized and discussed the available evidence supporting a strong association between accumulation of misfolded proteins and ER stress induction in several key neurodegenerative diseases. Although strong correlations exist between the misfolding and aggregation of an underlying protein and the presence of ER stress in neurodegenerative conditions, direct evidence to causally link the UPR and ER stress to neurological disorders *in vivo* is mostly lacking. Predicting whether and how ER stress affects is difficult because activation of the UPR may decrease neurodegeneration by increasing folding, protein quality control and autophagy, or extensive or chronic ER stress may result in irreversible neuronal damage and apoptosis. The mechanisms underlying modifications of ER homeostasis may differ in different disease contexts and include inhibition of ERAD function, perturbed vesicular trafficking, oxidative modifications of crucial ER foldases, and abnormal physical interactions with ER chaperones or UPR components (Figures 2 and 3). In addition, alterations in lipid, cholesterol or calcium metabolism may also affect ER function in many neurological disorders, contributing to the occurrence of ER stress.

Promising results have been obtained with pharmacological strategies to target ER stress in a disease context. Genetic manipulation of UPR components *in vivo* has been employed only in a few diseases to test the actual contribution of the pathway to neurodegeneration, and further efforts are needed to validate the role of ER stress in important diseases such as AD, PD and HD *in vivo*. Further we know little about the cell types in the brain that are primarily affected by ER stress nor have the endogenous stimuli that evoke the UPR been firmly identified. Neuronal populations with higher secretory requirements might display increased sensitivity to factors, genetic and environmental, that disrupt ER function. In this context, understanding the possible role of ER stress in cells such as oligodendrocytes, Schwann cells, or neuropeptide-secretory neurons is of particular relevance for future therapeutic intervention.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Kopito RR, Ron D: **Conformational disease**. *Nat Cell Biol* 2000, **2**:E207-209.

2. Rao RV, Bredesen DE: **Misfolded proteins, endoplasmic reticulum stress and neurodegeneration**. *Curr Opin Cell Biol* 2004, **16**:653-662.

3. Selkoe DJ: **Folding proteins in fatal ways**. *Nature* 2003, **426**:900-904.

4. Taylor JP, Hardy J, Fischbeck KH: **Toxic proteins in neurodegenerative disease**. *Science* 2002, **296**:1991-1995.

5. Ron D, Walter P: **Signal integration in the endoplasmic reticulum unfolded protein response**. *Nat Rev Mol Cell Biol* 2007, **8**:519-529.

6. Vembar SS, Brodsky JL: **One step at a time: endoplasmic reticulum-associated degradation**. *Nat Rev Mol Cell Biol* 2008, **9**:944-957.

7. Calfon M, Zeng H, Urano F, Till JH, Hubbard SR, Harding HP, Clark SG, Ron D: **IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA**. *Nature* 2002, **415**:92-96.

8. Lee K, Tirasophon W, Shen X, Michalak M, Prywes R, Okada T, Yoshida H, Mori K, Kaufman RJ: **IRE1-mediated unconventional mRNA splicing and S2P-mediated ATF6 cleavage merge to regulate XBP1 in signaling the unfolded protein response**. *Genes Dev* 2002, **16**:452-466.

9. Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K: **XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor**. *Cell* 2001, **107**:881-891.

10. Hetz C, Bernasconi P, Fisher J, Lee AH, Bassik MC, Antonsson B, Brandt GS, Iwakoshi NN, Schinzel A, Glimcher LH *et al.*: **Proapoptotic BAX and BAK modulate the unfolded protein response by a direct interaction with IRE1alpha**. *Science* 2006, **312**:572-576.

11. Lisbona F, Rojas-Rivera D, Thielen P, Zamorano S, Todd D, Martinon F, Glavic A, Kress C, Lin JH, Walter P *et al.*: **BAX inhibitor-1 is a negative regulator of the ER stress sensor IRE1alpha**. *Mol Cell* 2009, **33**:679-691.

12. Hetz C, Glimcher LH: **Fine-tuning of the unfolded protein response: assembling the IRE1alpha interactome**. *Mol Cell* 2009, **35**:551-561.

13. Hetz CaG L: **The UPRosome and XBP-1: mastering secretory cell function**. *Curr Immunol Rev* 2008, **4**:1-10.

14. Kim I, Shu CW, Xu W, Shiau CW, Grant D, Vasile S, Cosford ND, Reed JC: **Chemical biology investigation of cell death pathways activated by endoplasmic reticulum stress reveals cytoprotective modulators of ASK1**. *J Biol Chem* 2009, **284**:1593-1603.

15. Nishitoh H, Matsuzawa A, Tobiume K, Saegusa K, Takeda K, Inoue K, Hori S, Kakizuka A, Ichijo H: **ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats**. *Genes Dev* 2002, **16**:1345-1355.

16. Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, Harding HP, Ron D: **Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1**. *Science* 2000, **287**:664-666.

17. Ogata M, Hino S, Saito A, Morikawa K, Kondo S, Kanemoto S, Murakami T, Taniguchi M, Tanii I, Yoshinaga K *et al.*: **Autophagy is activated for cell survival after endoplasmic reticulum stress**. *Mol Cell Biol* 2006, **26**:9220-9231.

18. Levine B, Kroemer G: **Autophagy in the pathogenesis of disease**. *Cell* 2008, **132**:27-42.

19. Blais JD, Addison CL, Edge R, Falls T, Zhao H, Wary K, Koumenis C, Harding HP, Ron D, Holcik M *et al.*: **Perk-dependent translational regulation promotes tumor cell adaptation and angiogenesis in response to hypoxic stress**. *Mol Cell Biol* 2006, **26**:9517-9532.

20. Harding HP, Zhang Y, Ron D: **Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase**. *Nature* 1999, **397**:271-274.

21. Ameri K, Harris AL: **Activating transcription factor 4**. *Int J Biochem Cell Biol* 2008, **40**:14-21.

22. Harding HP, Zhang Y, Zeng H, Novoa I, Lu PD, Calfon M, Sadri N, Yun C, Popko B, Paules R *et al.*: **An integrated stress response regulates amino acid metabolism and resistance to oxidative stress**. *Mol Cell* 2003, **11**:619-633.

23. Lange PS, Chavez JC, Pinto JT, Coppola G, Sun CW, Townes TM, Geschwind DH, Ratan RR: **ATF4 is an oxidative stress-inducible, prodeath transcription factor in neurons *in vitro* and *in vivo***. *J Exp Med* 2008, **205**:1227-1242.

24. Kouroku Y, Fujita E, Tanida I, Ueno T, Isoai A, Kumagai H, Ogawa S, Kaufman RJ, Kominami E, Momoi T: **ER stress (PERK/eIF2alpha phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation**. *Cell Death Differ* 2007, **14**:230-239.

25. • Rouschop KM, van den Beucken T, Dubois L, Niessen H, Bussink J, Savelkouls K, Keulers T, Mujcic H, Landuyt W, Voncken JW *et al.*: **The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5**. *J Clin Invest* 2010, **120**:127-141.
This study reports that the UPR enhances the capacity of hypoxic tumor cells to undergo autophagy, and that this cellular process promotes their survival. The authors show ATF4 and CHOP, which are regulated by the UPR sensor PERK, modulates autophagy. This report support concept of interplay between distinct cellular defense mechanisms.

26. Rzymski T, Milani M, Pike L, Buffa F, Mellor HR, Winchester L, Pires I, Hammond E, Ragoussis I, Harris AL: **Regulation of autophagy by ATF4 in response to severe hypoxia**. *Oncogene* 2010, **29**:4424-4435.

27. Chen X, Shen J, Prywes R: **The luminal domain of ATF6 senses endoplasmic reticulum (ER) stress and causes translocation of ATF6 from the ER to the Golgi**. *J Biol Chem* 2002, **277**:13045-13052.

28. Haze K, Yoshida H, Yanagi H, Yura T, Mori K: **Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress**. *Mol Biol Cell* 1999, **10**:3787-3799.

29. Hetz CA: **ER stress signaling and the BCL-2 family of proteins: from adaptation to irreversible cellular damage**. *Antioxid Redox Signal* 2007, **9**:2345-2355.

30. Schroder M, Kaufman RJ: **The mammalian unfolded protein response**. *Annu Rev Biochem* 2005, **74**:739-789.

31. Heath-Engel HM, Chang NC, Shore GC: **The endoplasmic reticulum in apoptosis and autophagy: role of the BCL-2 protein family**. *Oncogene* 2008, **27**:6419-6433.

32. Hetz C, Glimcher L: **The daily job of night killers: alternative roles of the BCL-2 family in organelle physiology**. *Trends Cell Biol* 2008, **18**:38-44.

33. Xu C, Bailly-Maitre B, Reed JC: **Endoplasmic reticulum stress: cell life and death decisions**. *J Clin Invest* 2005, **115**:2656-2664.

34. Lin JH, Li H, Zhang Y, Ron D, Walter P: **Divergent effects of PERK and IRE1 signaling on cell viability**. *PLoS One* 2009, **4**:e4170.

35. Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, Jungreis R, Nagata K, Harding HP, Ron D: **CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum**. *Genes Dev* 2004, **18**:3066-3077.

36. McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ: **Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state**. *Mol Cell Biol* 2001, **21**:1249-1259.

37. Puthalakath H, O'Reilly LA, Gunn P, Lee L, Kelly PN, Huntington ND, Hughes PD, Michalak EM, McKimm-Breschkin J, Motoyama N *et al.*: **ER stress triggers apoptosis by activating BH3-only protein Bim**. *Cell* 2007, **129**:1337-1349.

38. Hotamisligil GS: **Endoplasmic reticulum stress and the inflammatory basis of metabolic disease**. *Cell* 2010, 140:900–917.

39. Todd DJ, Lee AH, Glimcher LH: **The endoplasmic reticulum stress response in immunity and autoimmunity**. *Nat Rev Immunol* 2008, **8**:663-674.

40. Kakiuchi C, Iwamoto K, Ishiwata M, Bundo M, Kasahara T, Kusumi I, Tsujita T, Okazaki Y, Nanko S, Kunugi H *et al.*: **Impaired feedback regulation of XBP1 as a genetic risk factor for bipolar disorder**. *Nat Genet* 2003, **35**:171-175.

41. Kato T, Kuratomi G, Kato N: **Genetics of bipolar disorder**. *Drugs Today (Barc)* 2005, **41**:335-344.

42. Kakiuchi C, Ishiwata M, Umekage T, Tochigi M, Kohda K, Sasaki T, Kato T: **Association of the XBP1-116C/G polymorphism with schizophrenia in the Japanese population**. *Psychiatry Clin Neurosci* 2004, **58**:438-440.

43. Kakiuchi C, Kato T: **Lithium response and −116C/G polymorphism of XBP1 in Japanese patients with bipolar disorder**. *Int J Neuropsychopharmacol* 2005, **8**:631-632.

44. Kato C, Kakiuchi C, Umekage T, Tochigi M, Kato N, Kato T, Sasaki T: **XBP1 gene polymorphism (−116C/G) and personality**. *Am J Med Genet B Neuropsychiatr Genet* 2005, **136B**:103-105.

45. Cao Y, Knochel S, Oswald F, Donow C, Zhao H, Knochel W: **XBP1 forms a regulatory loop with BMP-4 and suppresses mesodermal and neural differentiation in *Xenopus* embryos**. *Mech Dev* 2006, **123**:84-96.

46. Shim J, Umemura T, Nothstein E, Rongo C: **The unfolded protein response regulates glutamate receptor export from the endoplasmic reticulum**. *Mol Biol Cell* 2004, **15**:4818-4828.

47. Hayashi A, Kasahara T, Iwamoto K, Ishiwata M, Kametani M, Kakiuchi C, Furuichi T, Kato T: **The role of brain-derived neurotrophic factor (BDNF)-induced XBP1 splicing during brain development**. *J Biol Chem* 2007, **282**:34525-34534.

48. Murakami T, Hino SI, Saito A, Imaizumi K: **Endoplasmic reticulum stress response in dendrites of cultured primary neurons**. *Neuroscience* 2007, **146**:1-8.

49. Hayashi A, Kasahara T, Kametani M, Kato T: **Attenuated BDNF-induced upregulation of GABAergic markers in neurons lacking Xbp1**. *Biochem Biophys Res Commun* 2008, **376**:758-763.

50. Hoeffer CA, Klann E: **Switching gears: translational mastery of transcription during memory formation**. *Neuron* 2007, **54**:186-189.

51. Chen A, Muzzio IA, Malleret G, Bartsch D, Verbitsky M, Pavlidis P, Yonan AL, Vronskaya S, Grody MB, Cepeda I *et al.*: **Inducible enhancement of memory storage and synaptic plasticity in transgenic mice expressing an inhibitor of ATF4 (CREB-2) and C/EBP proteins**. *Neuron* 2003, **39**:655-669.

52. Costa-Mattioli M, Gobert D, Harding H, Herdy B, Azzi M, Bruno M, Bidinosti M, Ben Mamou C, Marcinkiewicz E, Yoshida M *et al.*: **Translational control of hippocampal synaptic plasticity and memory by the eIF2alpha kinase GCN2**. *Nature* 2005, **436**:1166-1173.

53. Costa-Mattioli M, Gobert D, Stern E, Gamache K, Colina R, Cuello C, Sossin W, Kaufman R, Pelletier J, Rosenblum K *et al.*: **eIF2alpha phosphorylation bidirectionally regulates the switch from short- to long-term synaptic plasticity and memory**. *Cell* 2007, **129**:195-206.

54. Nosyreva E, Kavalali ET: **Activity-dependent augmentation of spontaneous neurotransmission during endoplasmic reticulum stress**. *J Neurosci* 2010, **30**:7358-7368.

55. Pasinelli P, Brown RH: **Molecular biology of amyotrophic lateral sclerosis: insights from genetics**. *Nat Rev Neurosci* 2006, **7**:710-723.

56. Rowland LP, Shneider NA: **Amyotrophic lateral sclerosis**. *N Engl J Med* 2001, **344**:1688-1700.

57. Boillee S, Vande Velde C, Cleveland DW: **ALS: a disease of motor neurons and their nonneuronal neighbors**. *Neuron* 2006, **52**:39-59.

58. Cozzolino M, Ferri A, Carri MT: **Amyotrophic lateral sclerosis: from current developments in the laboratory to clinical implications**. *Antioxid Redox Signal* 2008, **10**:405-443.

59. Dupuis L, Muller A, Meininger V, Loeffler JP: **Molecular mechanisms of amyotrophic lateral sclerosis: recent contributions from studies in animal models**. *Rev Neurol (Paris)* 2004, **160**:35-43.

60. Nassif M, Matus S, Castillo K, Hetz C: **Amyotrophic lateral sclerosis pathogenesis: a journey through the secretory pathway**. *Antioxid Redox Signal* 2010, **13**:1955-1989.

61. Atkin JD, Farg MA, Walker AK, McLean C, Tomas D, Horne MK: **Endoplasmic reticulum stress and induction of the unfolded protein response in human sporadic amyotrophic lateral sclerosis**. *Neurobiol Dis* 2008, **30**:400-407.

62. •• Hetz C, Thielen P, Matus S, Nassif M, Court F, Kiffin R, Martinez G, Cuervo AM, Brown RH, Glimcher LH: **XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy**. *Genes Dev* 2009, **23**:2294-2306.
This study shows that genetic manipulation of the UPR transcription factor XBP-1 causes a massive increase in autophagy in motoneurons, enhancing the clearance of mutant SOD1 aggregates, and delays the development of amyotrophic lateral sclerosis in a SOD1 transgenic mouse. These findings suggest the existence of a homeostatic balance between distinct cellular protein homeostasis mechanisms.

63. Ilieva EV, Ayala V, Jove M, Dalfo E, Cacabelos D, Povedano M, Bellmunt MJ, Ferrer I, Pamplona R, Portero-Otin M: **Oxidative and endoplasmic reticulum stress interplay in sporadic amyotrophic lateral sclerosis**. *Brain* 2007, **130**:3111-3123.

64. Ito Y, Yamada M, Tanaka H, Aida K, Tsuruma K, Shimazawa M, Hozumi I, Inuzuka T, Takahashi H, Hara H: **Involvement of CHOP, an ER-stress apoptotic mediator, in both human sporadic ALS and ALS model mice**. *Neurobiol Dis* 2009, **36**:470-476.

65. Sasaki S: **Endoplasmic reticulum stress in motor neurons of the spinal cord in sporadic amyotrophic lateral sclerosis**. *J Neuropathol Exp Neurol* 2010, **69**:346-355.

66. Bosco DA, Morfini G, Karabacak NM, Song Y, Gros-Louis F, Pasinelli P, Goolsby H, Fontaine BA, Lemay N, McKenna-Yasek D *et al.*: **Wild-type and mutant SOD1 share an aberrant conformation and a common pathogenic pathway in ALS**. *Nat Neurosci* 2010, **13**:1396-1403.

67. Atkin JD, Farg MA, Turner BJ, Tomas D, Lysaght JA, Nunan J, Rembach A, Nagley P, Beart PM, Cheema SS *et al.*: **Induction of the unfolded protein response in familial amyotrophic lateral sclerosis and association of protein-disulfide isomerase with superoxide dismutase 1**. *J Biol Chem* 2006, **281**:30152-30165.

68. Kieran D, Woods I, Villunger A, Strasser A, Prehn JH: **Deletion of the BH3-only protein puma protects motoneurons from ER stress-induced apoptosis and delays motoneuron loss in ALS mice**. *Proc Natl Acad Sci U S A* 2007, **104**:20606-20611.

69. Kikuchi H, Almer G, Yamashita S, Guegan C, Nagai M, Xu Z, Sosunov AA, McKhann GM 2nd, Przedborski S: **Spinal cord endoplasmic reticulum stress associated with a microsomal accumulation of mutant superoxide dismutase-1 in an ALS model**. *Proc Natl Acad Sci U S A* 2006, **103**:6025-6030.

70. Nagata T, Ilieva H, Murakami T, Shiote M, Narai H, Ohta Y, Hayashi T, Shoji M, Abe K: **Increased ER stress during motor neuron degeneration in a transgenic mouse model of amyotrophic lateral sclerosis**. *Neurol Res* 2007, **29**:767-771.

71. • Nishitoh H, Kadowaki H, Nagai A, Maruyama T, Yokota T, Fukutomi H, Noguchi T, Matsuzawa A, Takeda K, Ichijo H: **ALS-linked mutant SOD1 induces ER stress- and ASK1-dependent motor neuron death by targeting Derlin-1**. *Genes Dev* 2008, **22**:1451-1464.
This report demonstrates that mutant SOD1 induces ER stress in part by interacting and blocking Derlin-1, an essential component of ER-associated degradation (ERAD) machinery. They also show that targeting ASK1 delays experimental ALS.

72. •• Saxena S, Cabuy E, Caroni P: **A role for motoneuron subtype-selective ER stress in disease manifestations of FALS mice**. *Nat Neurosci* 2009, **12**:627-636.
Using laser micro-dissection of motoneurons from wild-type and SOD1G93A transgenic ALS mice combined with gene expression profiling, this study indicate that vulnerable motoneurons are particularly prone to undergo chronic ER stress. Using a pharmacological agent to target the eIF2α pathway, they observed protection against experimental ALS. This study, together with reference [62••], demonstrated the importance of the UPR on ALS and indicates that different UPR signaling branches have distinct and contrasting effects on disease progression.

73. Walker AK, Farg MA, Bye CR, McLean CA, Horne MK, Atkin JD: **Protein disulphide isomerase protects against protein aggregation and is S-nitrosylated in amyotrophic lateral sclerosis**. *Brain* 2010, **133**:105-116.

74. Wootz H, Hansson I, Korhonen L, Lindholm D: **XIAP decreases caspase-12 cleavage and calpain activity in spinal cord of ALS transgenic mice**. *Exp Cell Res* 2006, **312**:1890-1898.

75. Urushitani M, Ezzi SA, Matsuo A, Tooyama I, Julien JP: **The endoplasmic reticulum-Golgi pathway is a target for translocation and aggregation of mutant superoxide dismutase linked to ALS**. *Faseb J* 2008, **22**:2476-2487.

76. Urushitani M, Sik A, Sakurai T, Nukina N, Takahashi R, Julien JP: **Chromogranin-mediated secretion of mutant superoxide dismutase proteins linked to amyotrophic lateral sclerosis**. *Nat Neurosci* 2006, **9**:108-118.

77. Boyce M, Bryant KF, Jousse C, Long K, Harding HP, Scheuner D, Kaufman RJ, Ma D, Coen DM, Ron D *et al.*: **A selective inhibitor of eIF2alpha dephosphorylation protects cells from ER stress**. *Science* 2005, **307**:935-939.

78. Shimazawa M, Tanaka H, Ito Y, Morimoto N, Tsuruma K, Kadokura M, Tamura S, Inoue T, Yamada M, Takahashi H *et al.*: **An inducer of VGF protects cells against ER stress-induced cell death and prolongs survival in the mutant SOD1 animal models of familial ALS**. *PLoS One* 2010, **5**:e15307.

79. Nishimura AL, Mitne-Neto M, Silva HC, Richieri-Costa A, Middleton S, Cascio D, Kok F, Oliveira JR, Gillingwater T, Webb J *et al.*: **A mutation in the vesicle-trafficking protein VAPB causes late-onset spinal muscular atrophy and amyotrophic lateral sclerosis**. *Am J Hum Genet* 2004, **75**:822-831.

80. Gkogkas C, Middleton S, Kremer AM, Wardrope C, Hannah M, Gillingwater TH, Skehel P: **VAPB interacts with and modulates the activity of ATF6**. *Hum Mol Genet* 2008, **17**:1517-1526.

81. Langou K, Moumen A, Pellegrino C, Aebischer J, Medina I, Aebischer P, Raoul C: **AAV-mediated expression of wild-type and ALS-linked mutant VAPB selectively triggers death of motoneurons through a Ca^{2+}-dependent ER-associated pathway**. *J Neurochem* 2010, **114**:795-809.

82. Teuling E, Ahmed S, Haasdijk E, Demmers J, Steinmetz MO, Akhmanova A, Jaarsma D, Hoogenraad CC: **Motor neuron disease-associated mutant vesicle-associated membrane protein-associated protein (VAP) B recruits wild-type VAPs into endoplasmic reticulum-derived tubular aggregates**. *J Neurosci* 2007, **27**:9801-9815.

83. Suzuki H, Kanekura K, Levine TP, Kohno K, Olkkonen VM, Aiso S, Matsuoka M: **ALS-linked P56S-VAPB, an aggregated loss-of-function mutant of VAPB, predisposes motor neurons to ER stress-related death by inducing aggregation of co-expressed wild-type VAPB**. *J Neurochem* 2009, **108**:973-985.

84. Mackenzie IR, Rademakers R, Neumann M: **TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia**. *Lancet Neurol* 2010, **9**:995-1007.

85. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM *et al.*: **Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis**. *Science* 2006, **314**:130-133.

86. Shan X, Chiang PM, Price DL, Wong PC: **Altered distributions of Gemini of coiled bodies and mitochondria in motor neurons of**

TDP-43 transgenic mice. *Proc Natl Acad Sci U S A* 2010, **107**:16325-16330.

87. Kwiatkowski TJ Jr, Bosco DA, Leclerc AL, Tamrazian E, Vanderburg CR, Russ C, Davis A, Gilchrist J, Kasarskis EJ, Munsat T *et al.*: **Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis**. *Science* 2009, **323**:1205-1208.

88. Deng HX, Zhai H, Bigio EH, Yan J, Fecto F, Ajroud K, Mishra M, Ajroud-Driss S, Heller S, Sufit R *et al.*: **FUS-immunoreactive inclusions are a common feature in sporadic and non-SOD1 familial amyotrophic lateral sclerosis**. *Ann Neurol* 2010, **67**:739-748.

89. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, Fratiglioni L, Lobo A, Martinez-Lage J, Trenkwalder C *et al.*: **Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group**. *Neurology* 2000, **54**:S21-23.

90. Klein C, Lohmann-Hedrich K: **Impact of recent genetic findings in Parkinson's disease**. *Curr Opin Neurol* 2007, **20**:453-464.

91. Conn KJ, Gao W, McKee A, Lan MS, Ullman MD, Eisenhauer PB, Fine RE, Wells JM: **Identification of the protein disulfide isomerase family member PDIp in experimental Parkinson's disease and Lewy body pathology**. *Brain Res* 2004, **1022**:164-172.

92. Hoozemans JJ, van Haastert ES, Eikelenboom P, de Vos RA, Rozemuller JM, Scheper W: **Activation of the unfolded protein response in Parkinson's disease**. *Biochem Biophys Res Commun* 2007, **354**:707-711.

93. Slodzinski H, Moran LB, Michael GJ, Wang B, Novoselov S, Cheetham ME, Pearce RK, Graeber MB: **Homocysteine-induced endoplasmic reticulum protein (herp) is up-regulated in parkinsonian substantia nigra and present in the core of Lewy bodies**. *Clin Neuropathol* 2009, **28**:333-343.

94. Makioka K, Yamazaki T, Fujita Y, Takatama M, Nakazato Y, Okamoto K: **Involvement of endoplasmic reticulum stress defined by activated unfolded protein response in multiple system atrophy**. *J Neurol Sci* 2010, **297**:60-65.

95. Uehara T, Nakamura T, Yao D, Shi ZQ, Gu Z, Ma Y, Masliah E, Nomura Y, Lipton SA: **S-nitrosylated protein-disulphide isomerase links protein misfolding to neurodegeneration**. *Nature* 2006, **441**:513-517.

96. Smith WW, Jiang H, Pei Z, Tanaka Y, Morita H, Sawa A, Dawson VL, Dawson TM, Ross CA: **Endoplasmic reticulum stress and mitochondrial cell death pathways mediate A53T mutant alpha-synuclein-induced toxicity**. *Hum Mol Genet* 2005, **14**:3801-3811.

97. Cooper AA, Gitler AD, Cashikar A, Haynes CM, Hill KJ, Bhullar B, Liu K, Xu K, Strathearn KE, Liu F *et al.*: **Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models**. *Science* 2006, **313**:324-328.

98. Gitler AD, Bevis BJ, Shorter J, Strathearn KE, Hamamichi S, Su LJ, Caldwell KA, Caldwell GA, Rochet JC, McCaffery JM *et al.*: **The Parkinson's disease protein alpha-synuclein disrupts cellular Rab homeostasis**. *Proc Natl Acad Sci U S A* 2008, **105**:145-150.

99. Ding WX, Yin XM: **Sorting, recognition and activation of the misfolded protein degradation pathways through macroautophagy and the proteasome**. *Autophagy* 2008, **4**:141-150.

100. Sugeno N, Takeda A, Hasegawa T, Kobayashi M, Kikuchi A, Mori F, Wakabayashi K, Itoyama Y: **Serine 129 phosphorylation of alpha-synuclein induces unfolded protein response-mediated cell death**. *J Biol Chem* 2008, **283**:23179-23188.

101. Imai Y, Soda M, Takahashi R: **Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity**. *J Biol Chem* 2000, **275**:35661-35664.

102. Tsai YC, Fishman PS, Thakor NV, Oyler GA: **Parkin facilitates the elimination of expanded polyglutamine proteins and leads to preservation of proteasome function**. *J Biol Chem* 2003, **278**:22044-22055.

103. Wang HQ, Imai Y, Kataoka A, Takahashi R: **Cell type-specific upregulation of Parkin in response to ER stress**. *Antioxid Redox Signal* 2007, **9**:533-542.

104. Kitao Y, Imai Y, Ozawa K, Kataoka A, Ikeda T, Soda M, Nakimawa K, Kiyama H, Stern DM, Hori O *et al.*: **Pael receptor induces death of dopaminergic neurons in the substantia nigra via endoplasmic reticulum stress and dopamine toxicity, which is enhanced under condition of parkin inactivation**. *Hum Mol Genet* 2007, **16**:50-60.

105. Kubota K, Niinuma Y, Kaneko M, Okuma Y, Sugai M, Omura T, Uesugi M, Uehara T, Hosoi T, Nomura Y: **Suppressive effects of 4-phenylbutyrate on the aggregation of Pael receptors and endoplasmic reticulum stress**. *J Neurochem* 2006, **97**:1259-1268.

106. Marazziti D, Di Pietro C, Golini E, Mandillo S, Matteoni R, Tocchini-Valentini GP: **Macroautophagy of the GPR37 orphan receptor and Parkinson disease-associated neurodegeneration**. *Autophagy* 2009, **5**:741-742.

107. Yokota T, Sugawara K, Ito K, Takahashi R, Ariga H, Mizusawa H: **Down regulation of DJ-1 enhances cell death by oxidative stress, ER stress, and proteasome inhibition**. *Biochem Biophys Res Commun* 2003, **312**:1342-1348.

108. Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J *et al.*: **Hereditary Parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase**. *Nat Genet* 2006, **38**:1184-1191.

109. Samann J, Hegermann J, von Gromoff E, Eimer S, Baumeister R, Schmidt E: ***Caenorhabditits elegans* LRK-1 and PINK-1 act antagonistically in stress response and neurite outgrowth**. *J Biol Chem* 2009, **284**:16482-16491.

110. Holtz WA, O'Malley KL: **Parkinsonian mimetics induce aspects of unfolded protein response in death of dopaminergic neurons**. *J Biol Chem* 2003, **278**:19367-19377.

111. Ryu EJ, Harding HP, Angelastro JM, Vitolo OV, Ron D, Greene LA: **Endoplasmic reticulum stress and the unfolded protein response in cellular models of Parkinson's disease**. *J Neurosci* 2002, **22**:10690-10698.

112. Silva RM, Ries V, Oo TF, Yarygina O, Jackson-Lewis V, Ryu EJ, Lu PD, Marciniak SJ, Ron D, Przedborski S *et al.*: **CHOP/GADD153 is a mediator of apoptotic death in substantia nigra dopamine neurons in an *in vivo* neurotoxin model of Parkinsonism**. *J Neurochem* 2005, **95**:974-986.

113. Sado M, Yamasaki Y, Iwanaga T, Onaka Y, Ibuki T, Nishihara S, Mizuguchi H, Momota H, Kishibuchi R, Hashimoto T *et al.*: **Protective effect against Parkinson's disease-related insults through the activation of XBP1**. *Brain Res* 2009, **1257**:16-24.

114. Egawa N, Yamamoto K, Inoue H, Hikawa R, Nishi K, Mori K, Takahashi R: **The endoplasmic reticulum stress sensor. ATF6{alpha}, protects against neurotoxin-induced dopaminergic neuronal death**. *J Biol Chem* 2010.

115. Holtz WA, Turetzky JM, Jong YJ, O'Malley KL: **Oxidative stress-triggered unfolded protein response is upstream of intrinsic cell death evoked by Parkinsonian mimetics**. *J Neurochem* 2006, **99**:54-69.

116. Cattaneo E, Zuccato C, Tartari M: **Normal huntingtin function: an alternative approach to Huntington's disease**. *Nat Rev Neurosci* 2005, **6**:919-930.

117. van Dellen A, Grote HE, Hannan AJ: **Gene–environment interactions, neuronal dysfunction and pathological plasticity in Huntington's disease**. *Clin Exp Pharmacol Physiol* 2005, **32**:1007-1019.

118. Nucifora FC Jr, Sasaki M, Peters MF, Huang H, Cooper JK, Yamada M, Takahashi H, Tsuji S, Troncoso J, Dawson VL *et al.*: **Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity**. *Science* 2001, **291**:2423-2428.

119. Rockabrand E, Natalia Slepko AP, Vidya NN, Aleksey K, Marsh JL, Sullivan GP, Steffan JS, Sensi SL, Michels Thompson L: **The first 17 amino acids of Huntingtin modulate its sub-cellular**

localization, aggregation and effects on calcium homeostasis. *Hum Mol Genet* 2007, **16**:61-77.

120. Wyttenbach A, Carmichael J, Swartz J, Furlong RA, Narain Y, Rankin J, Rubinsztein DC: **Effects of heat shock, heat shock protein 40 (HDJ-2), and proteasome inhibition on protein aggregation in cellular models of Huntington's disease**. *Proc Natl Acad Sci U S A* 2000, **97**:2898-2903.

121. Carnemolla A, Fossale E, Agostoni E, Michelazzi S, Calligaris R, De Maso L, Del Sal G, MacDonald ME, Persichetti F: **Rrs1 is involved in endoplasmic reticulum stress response in Huntington disease**. *J Biol Chem* 2009, **284**:18167-18173.

•122. Duennwald ML, Lindquist S: **Impaired ERAD and ER stress are early and specific events in polyglutamine toxicity**. *Genes Dev* 2008, **22**:3308-3319.

This study reveals a possibly mechanism underlying polyglutamine toxicity. They report that yeast cells and neuron-like PC12 cells expressing polyQ-expanded shows a defect in ERAD. This ERAD defect is mediated by the entrapment of essential ERAD components by polyQ-expanded Htt fragments, triggering ER stress.

123. Kouroku Y, Fujita E, Jimbo A, Kikuchi T, Yamagata T, Momoi MY, Kominami E, Kuida K, Sakamaki K, Yonehara S *et al.*: **Polyglutamine aggregates stimulate ER stress signals and caspase-12 activation**. *Hum Mol Genet* 2002, **11**:1505-1515.

124. Vidal R, Caballero B, Couve A, Hetz C: **Converging pathways in the occurrence of endoplasmic reticulum (ER) stress in Huntington's disease**. *Curr Mol Med* 2011, **11**:1-12.

125. Noh JY, Lee H, Song S, Kim NS, Im W, Kim M, Seo H, Chung CW, Chang JW, Ferrante RJ *et al.*: **SCAMP5 links endoplasmic reticulum stress to the accumulation of expanded polyglutamine protein aggregates via endocytosis inhibition**. *J Biol Chem* 2009, **284**:11318-11325.

126. Cho KJ, Lee BI, Cheon SY, Kim HW, Kim HJ, Kim GW: **Inhibition of apoptosis signal-regulating kinase 1 reduces endoplasmic reticulum stress and nuclear huntingtin fragments in a mouse model of Huntington disease**. *Neuroscience* 2009, **163**:1128-1134.

127. Atwal RS, Xia J, Pinchev D, Taylor J, Epand RM, Truant R: **Huntingtin has a membrane association signal that can modulate huntingtin aggregation, nuclear entry and toxicity**. *Hum Mol Genet* 2007, **16**:2600-2615.

128. Yang H, Liu C, Zhong Y, Luo S, Monteiro MJ, Fang S: **Huntingtin interacts with the cue domain of gp78 and inhibits gp78 binding to ubiquitin and p97/VCP**. *PLoS One* 2010, **5**:e8905.

129. Fernandez-Fernandez MR, Ferrer I, Lucas JJ: **Impaired ATF6alpha processing, decreased Rheb and neuronal cell cycle re-entry in Huntington's disease**. *Neurobiol Dis* 2011, **41**:23-32.

130. Prusiner SB: **Prions. Proc Natl Acad Sci U S A**1998, **95**:13363-13383.

131. Vey M, Pilkuhn S, Wille H, Nixon R, DeArmond SJ, Smart EJ, Anderson RG, Taraboulos A, Prusiner SB: **Subcellular colocalization of the cellular and scrapie prion proteins in caveolae-like membranous domains**. *Proc Natl Acad Sci U S A* 1996, **93**:14945-14949.

132. Hetz CA, Soto C: **Stressing out the ER: a role of the unfolded protein response in prion-related disorders**. *Curr Mol Med* 2006, **6**:37-43.

133. Pan KM, Baldwin M, Nguyen J, Gasset M, Serban A, Groth D, Mehlhorn I, Huang Z, Fletterick RJ, Cohen FE *et al.*: **Conversion of alpha-helices into beta-sheets features in the formation of the scrapie prion proteins**. *Proc Natl Acad Sci U S A* 1993, **90**:10962-10966.

134. Brown AR, Rebus S, McKimmie CS, Robertson K, Williams A, Fazakerley JK: **Gene expression profiling of the preclinical scrapie-infected hippocampus**. *Biochem Biophys Res Commun* 2005, **334**:86-95.

135. Hetz C, Lee AH, Gonzalez-Romero D, Thielen P, Castilla J, Soto C, Glimcher LH: **Unfolded protein response transcription factor XBP-1 does not influence prion replication or pathogenesis**. *Proc Natl Acad Sci U S A* 2008, **105**:757-762.

136. Hetz C, Russelakis-Carneiro M, Maundrell K, Castilla J, Soto C: **Caspase-12 and endoplasmic reticulum stress mediate neurotoxicity of pathological prion protein**. *Embo J* 2003, **22**:5435-5445.

137. Hetz C, Russelakis-Carneiro M, Walchli S, Carboni S, Vial-Knecht E, Maundrell K, Castilla J, Soto C: **The disulfide isomerase Grp58 is a protective factor against prion neurotoxicity**. *J Neurosci* 2005, **25**:2793-2802.

138. Rane NS, Kang SW, Chakrabarti O, Feigenbaum L, Hegde RS: **Reduced translocation of nascent prion protein during ER stress contributes to neurodegeneration**. *Dev Cell* 2008, **15**:359-370.

139. Steele AD, Hetz C, Yi CH, Jackson WS, Borkowski AW, Yuan J, Wollmann RH, Lindquist S: **Prion pathogenesis is independent of caspase-12**. *Prion* 2007, **1**:243-247.

140. Yoo BC, Krapfenbauer K, Cairns N, Belay G, Bajo M, Lubec G: **Overexpressed protein disulfide isomerase in brains of patients with sporadic Creutzfeldt-Jakob disease**. *Neurosci Lett* 2002, **334**:196-200.

141. Xu K, Wang X, Shi Q, Chen C, Tian C, Li XL, Zhou RM, Chu YL, Dong XP: **Human prion protein mutants with deleted and inserted octarepeats undergo different pathways to trigger cell apoptosis**. *J Mol Neurosci* 2011, **43**:225-234.

142. Apodaca J, Kim I, Rao H: **Cellular tolerance of prion protein PrP in yeast involves proteolysis and the unfolded protein response**. *Biochem Biophys Res Commun* 2006, **347**:319-326.

143. Hetz C, Castilla J, Soto C: **Perturbation of endoplasmic reticulum homeostasis facilitates prion replication**. *J Biol Chem* 2007, **282**:12725-12733.

144. Orsi A, Fioriti L, Chiesa R, Sitia R: **Conditions of endoplasmic reticulum stress favor the accumulation of cytosolic prion protein**. *J Biol Chem* 2006, **281**:30431-30438.

145. Ma J, Lindquist S: **Conversion of PrP to a self-perpetuating PrPSc-like conformation in the cytosol**. *Science* 2002, **298**:1785-1788.

146. Yedidia Y, Horonchik L, Tzaban S, Yanai A, Taraboulos A: **Proteasomes and ubiquitin are involved in the turnover of the wild-type prion protein**. *Embo J* 2001, **20**:5383-5391.

147. Citron M: **Alzheimer's disease: treatments in discovery and development**. *Nat Neurosci* 2002, **5(Suppl)**:1055-1057.

148. Haass C, Selkoe DJ: **Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide**. *Nat Rev Mol Cell Biol* 2007, **8**:101-112.

149. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J: **Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta**. *Nature* 2000, **403**:98-103.

150. Hitomi J, Katayama T, Eguchi Y, Kudo T, Taniguchi M, Koyama Y, Manabe T, Yamagishi S, Bando Y, Imaizumi K *et al.*: **Involvement of caspase-4 in endoplasmic reticulum stress-induced apoptosis and Abeta-induced cell death**. *J Cell Biol* 2004, **165**:347-356.

151. Hoozemans JJ, van Haastert ES, Nijholt DA, Rozemuller AJ, Eikelenboom P, Scheper W: **The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus**. *Am J Pathol* 2009, **174**:1241-1251.

152. Hoozemans JJ, Veerhuis R, Van Haastert ES, Rozemuller JM, Baas F, Eikelenboom P, Scheper W: **The unfolded protein response is activated in Alzheimer's disease**. *Acta Neuropathol* 2005, **110**:165-172.

153. Scheper W, Hoozemans JJ, Hoogenraad CC, Rozemuller AJ, Eikelenboom P, Baas F: **Rab6 is increased in Alzheimer's disease brain and correlates with endoplasmic reticulum stress**. *Neuropathol Appl Neurobiol* 2007, **33**:523-532.

154. Honjo Y, Ito H, Horibe T, Takahashi R, Kawakami K: **Protein disulfide isomerase-immunopositive inclusions in patients with Alzheimer disease**. *Brain Res* 2010, **1349**:90-96.

155. Lee JH, Won SM, Suh J, Son SJ, Moon GJ, Park UJ, Gwag BJ: **Induction of the unfolded protein response and cell death pathway in Alzheimer's disease, but not in aged Tg2576 mice**. *Exp Mol Med* 2010, **42**:386-394.

156. Chafekar SM, Zwart R, Veerhuis R, Vanderstichele H, Baas F, Scheper W: **Increased Abeta1-42 production sensitizes neuroblastoma cells for ER stress toxicity**. *Curr Alzheimer Res* 2008, **5**:469-474.

157. De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, Klein WL: **Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine**. *J Biol Chem* 2007, **282**:11590-11601.

158. Ferreiro E, Oliveira CR, Pereira C: **Involvement of endoplasmic reticulum Ca^{2+} release through ryanodine and inositol 1,4,5-triphosphate receptors in the neurotoxic effects induced by the amyloid-beta peptide**. *J Neurosci Res* 2004, **76**:872-880.

159. Kaneko M, Koike H, Saito R, Kitamura Y, Okuma Y, Nomura Y: **Loss of HRD1-mediated protein degradation causes amyloid precursor protein accumulation and amyloid-beta generation**. *J Neurosci* 2010, 30:3924–3932.

160. Kosuge Y, Sakikubo T, Ishige K, Ito Y: **Comparative study of endoplasmic reticulum stress-induced neuronal death in rat cultured hippocampal and cerebellar granule neurons**. *Neurochem Int* 2006, **49**:285-293.

161. Lee do Y, Lee KS, Lee HJ, Kim do H, Noh YH, Yu K, Jung HY, Lee SH, Lee JY, Youn YC *et al.*: **Activation of PERK signaling attenuates Abeta-mediated ER stress**. *PLoS One* 2010, **5**:e10489.

162. Nishitsuji K, Tomiyama T, Ishibashi K, Ito K, Teraoka R, Lambert MP, Klein WL, Mori H: **The E693Delta mutation in amyloid precursor protein increases intracellular accumulation of amyloid beta oligomers and causes endoplasmic reticulum stress-induced apoptosis in cultured cells**. *Am J Pathol* 2009, **174**:957-969.

163. Resende R, Ferreiro E, Pereira C, Oliveira CR: **ER stress is involved in Abeta-induced GSK-3beta activation and tau phosphorylation**. *J Neurosci Res* 2008, **86**:2091-2099.

164. Song S, Lee H, Kam TI, Tai ML, Lee JY, Noh JY, Shim SM, Seo SJ, Kong YY, Nakagawa T *et al.*: **E2-25K/Hip-2 regulates caspase-12 in ER stress-mediated Abeta neurotoxicity**. *J Cell Biol* 2008, **182**:675-684.

165. Wiley JC, Meabon JS, Frankowski H, Smith EA, Schecterson LC, Bothwell M, Ladiges WC: **Phenylbutyric acid rescues endoplasmic reticulum stress-induced suppression of APP proteolysis and prevents apoptosis in neuronal cells**. *PLoS One* 2010, **5**:e9135.

166. Ghribi O, Herman MM, Savory J: **Lithium inhibits Abeta-induced stress in endoplasmic reticulum of rabbit hippocampus but does not prevent oxidative damage and tau phosphorylation**. *J Neurosci Res* 2003, **71**:853-862.

167. Heinitz K, Beck M, Schliebs R, Perez-Polo JR: **Toxicity mediated by soluble oligomers of beta-amyloid(1–42) on cholinergic SN56.B5.G4 cells**. *J Neurochem* 2006, **98**:1930-1945.

168. Ghribi O, Herman MM, DeWitt DA, Forbes MS, Savory J: **Abeta(1–42) and aluminum induce stress in the endoplasmic reticulum in rabbit hippocampus, involving nuclear translocation of gadd 153 and NF-kappaB**. *Brain Res Mol Brain Res* 2001, **96**:30-38.

169. Ghribi O, Herman MM, Pramoonjago P, Spaulding NK, Savory J: **GDNF regulates the A beta-induced endoplasmic reticulum stress response in rabbit hippocampus by inhibiting the activation of gadd 153 and the JNK and ERK kinases**. *Neurobiol Dis* 2004, **16**:417-427.

170. Selwood SP, Parvathy S, Cordell B, Ryan HS, Oshidari F, Vincent V, Yesavage J, Lazzeroni LC, Murphy GM Jr: **Gene expression profile of the PDAPP mouse model for Alzheimer's disease with and without Apolipoprotein E**. *Neurobiol Aging* 2009, **30**:574-590.

171. Sano R, Annunziata I, Patterson A, Moshiach S, Gomero E, Opferman J, Forte M, d'Azzo A: **GM1-ganglioside accumulation at the mitochondria-associated ER membranes links ER stress to Ca(2+)-dependent mitochondrial apoptosis**. *Mol Cell* 2009, **36**:500-511.

172. Tessitore A, del PMM, Sano R, Ma Y, Mann L, Ingrassia A, Laywell ED, Steindler DA, Hendershot LM, d'Azzo A: **GM1-ganglioside-mediated activation of the unfolded protein response causes neuronal death in a neurodegenerative gangliosidosis**. *Mol Cell* 2004, **15**:753-766.

173. Wei H, Kim SJ, Zhang Z, Tsai PC, Wisniewski KE, Mukherjee AB: **ER and oxidative stresses are common mediators of apoptosis in both neurodegenerative and non-neurodegenerative lysosomal storage disorders and are alleviated by chemical chaperones**. *Hum Mol Genet* 2008, **17**:469-477.

174. Zhang Z, Lee YC, Kim SJ, Choi MS, Tsai PC, Xu Y, Xiao YJ, Zhang P, Heffer A, Mukherjee AB: **Palmitoyl-protein thioesterase-1 deficiency mediates the activation of the unfolded protein response and neuronal apoptosis in INCL**. *Hum Mol Genet* 2006, **15**:337-346.

175. Farfel-Becker T, Vitner E, Dekel H, Leshem N, Enquist IB, Karlsson S, Futerman AH: **No evidence for activation of the unfolded protein response in neuronopathic models of Gaucher disease**. *Hum Mol Genet* 2009, **18**:1482-1488.

176. Klein A, Mosqueira M, Martinez G, Robledo F, González M, Caballero B, Cancino G, Alvarez A, Hetz C, Zanlungo S: **Lack of activation of the Unfolded Protein Response (UPR) in mouse and cellular models of Niemann-Pick type C disease**. *Neurodeg Dis* 2011, **8**:124-128.

177. Aufenberg C, Wenkel S, Mautes A, Paschen W: **Spinal cord trauma activates processing of xbp1 mRNA indicative of endoplasmic reticulum dysfunction**. *J Neurotrauma* 2005, **22**:1018-1024.

178. Penas C, Guzman MS, Verdu E, Fores J, Navarro X, Casas C: **Spinal cord injury induces endoplasmic reticulum stress with different cell-type dependent response**. *J Neurochem* 2007, **102**:1242-1255.

179. Wan S, Shi P, Zhang X, Gu C, Fan S: **Stronger expression of CHOP and caspase 12 in diabetic spinal cord injury rats**. *Neurol Res* 2009, **31**:1049-1055.

180. Yamauchi T, Sakurai M, Abe K, Matsumiya G, Sawa Y: **Impact of the endoplasmic reticulum stress response in spinal cord after transient ischemia**. *Brain Res* 2007, **1169**:24-33.

181. Mizukami T, Orihashi K, Herlambang B, Takahashi S, Hamaishi M, Okada K, Sueda T: **Sodium 4-phenylbutyrate protects against spinal cord ischemia by inhibition of endoplasmic reticulum stress**. *J Vasc Surg* 2010, **52**:1580-1586.

182. Lin W, Popko B: **Endoplasmic reticulum stress in disorders of myelinating cells**. *Nat Neurosci* 2009, **12**:379-385.

183. Lees JR, Cross AH: **A little stress is good: IFN-gamma, demyelination, and multiple sclerosis**. *J Clin Invest* 2007, **117**:297-299.

184. Lin W, Harding HP, Ron D, Popko B: **Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-gamma**. *J Cell Biol* 2005, **169**:603-612.

185. Lin W, Kemper A, Dupree JL, Harding HP, Ron D, Popko B: **Interferon-gamma inhibits central nervous system remyelination through a process modulated by endoplasmic reticulum stress**. *Brain* 2006, **129**:1306-1318.

186. Lin W, Kunkler PE, Harding HP, Ron D, Kraig RP, Popko B: **Enhanced integrated stress response promotes myelinating oligodendrocyte survival in response to interferon-gamma**. *Am J Pathol* 2008, **173**:1508-1517.

187. Mhaille AN, McQuaid S, Windebank A, Cunnea P, McMahon J, Samali A, FitzGerald U: **Increased expression of endoplasmic reticulum stress-related signaling pathway molecules in multiple sclerosis lesions**. *J Neuropathol Exp Neurol* 2008, **67**:200-211.

188. Ramagopalan SV, Dobson R, Meier UC, Giovannoni G: **Multiple sclerosis: risk factors, prodromes, and potential causal pathways**. *Lancet Neurol* 2010, **9**:727-739.

189. Pennuto M, Tinelli E, Malaguti M, Del Carro U, D'Antonio M, Ron D,
• Quattrini A, Feltri ML, Wrabetz L: **Ablation of the UPR-mediator CHOP restores motor function and reduces demyelination in Charcot-Marie-Tooth 1B mice**. *Neuron* 2008, **57**:393-405.
This article studies the human neuropathy Charcot-Marie-Tooth 1B disease in a mouse model expressing a deleted form of the myelin P0 protein (S63del mice). They observed UPR activation on the model, including the expression of CHOP protein. Chop ablation in S63del mice completely rescued motor deficits, in addition to electrophysiological and morphological abnormalities. These results indicate that signaling through the CHOP arm of the UPR provokes demyelination in inherited neuropathy and suggesting a novel pathogenic role of chronic ER stress in demyelinating peripheral neuropathies.

190. Southwood CM, Garbern J, Jiang W, Gow A: **The unfolded protein response modulates disease severity in Pelizaeus-Merzbacher disease**. *Neuron* 2002, **36**:585-596.

191. Kantor L, Harding HP, Ron D, Schiffmann R, Kaneski CR, Kimball SR, Elroy-Stein O: **Heightened stress response in primary fibroblasts expressing mutant eIF2B genes from CACH/VWM leukodystrophy patients**. *Hum Genet* 2005, **118**:99-106.

192. Kantor L, Pinchasi D, Mintz M, Hathout Y, Vanderver A, Elroy-Stein O: **A point mutation in translation initiation factor 2B leads to a continuous hyper stress state in oligodendroglial-derived cells**. *PLoS One* 2008, **3**:e3783.

193. Gorbatyuk MS, Knox T, LaVail MM, Gorbatyuk OS, Noorwez SM, Hauswirth WW, Lin JH, Muzyczka N, Lewin AS: **Restoration of visual function in P23H rhodopsin transgenic rats by gene delivery of BiP/Grp78**. *Proc Natl Acad Sci U S A* 2010, **107**:5961-5966.

194. Kang MJ, Ryoo HD: **Suppression of retinal degeneration in**
• **Drosophila by stimulation of ER-associated degradation**. *Proc Natl Acad Sci U S A* 2009, **106**:17043-17048.
This study reports the participation of the ERAD pathway in a fly model of autosomal dominant retinitis pigmentosa (ADRP), cused by mutant forms of rhodopsin-1 protein. This study shows that the co-expression of certain ERAD factors was sufficient to reduce mutant rhodopsin-1 protein levels and to completely suppress ER stress. These results indicate that the ERAD pathway has a protective mechanism against retinal degeneration. Along with Ref. [122•], this study suggests that manipulation of ERAD may serve as a powerful therapeutic strategy against a number of diseases associated with ER stress.

195. Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, Panning B, Shokat KM, Lavail MM, Walter P: **IRE1 signaling affects cell fate during the unfolded protein response**. *Science* 2007, **318**:944-949.

196. Mendes CS, Levet C, Chatelain G, Dourlen P, Fouillet A, Dichtel-Danjoy ML, Gambis A, Ryoo HD, Steller H, Mollereau B: **ER stress protects from retinal degeneration**. *Embo J* 2009, **28**:1296-1307.

197. Ryoo HD, Domingos PM, Kang MJ, Steller H: **Unfolded protein response in a Drosophila model for retinal degeneration**. *Embo J* 2007, **26**:242-252.

198. Bonapace G, Waheed A, Shah GN, Sly WS: **Chemical chaperones protect from effects of apoptosis-inducing mutation in carbonic anhydrase IV identified in retinitis pigmentosa 17**. *Proc Natl Acad Sci U S A* 2004, **101**:12300-12305.

199. Datta R, Waheed A, Bonapace G, Shah GN, Sly WS: **Pathogenesis of retinitis pigmentosa associated with apoptosis-inducing mutations in carbonic anhydrase IV**. *Proc Natl Acad Sci U S A* 2009, **106**:3437-3442.

200. Rebello G, Ramesar R, Vorster A, Roberts L, Ehrenreich L, Oppon E, Gama D, Bardien S, Greenberg J, Bonapace G *et al.*: **Apoptosis-inducing signal sequence mutation in carbonic anhydrase IV identified in patients with the RP17 form of retinitis pigmentosa**. *Proc Natl Acad Sci U S A* 2004, **101**:6617-6622.