Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases

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Abstract | The unfolded protein response (UPR) is a homeostatic mechanism by which cells regulate levels of misfolded proteins in the endoplasmic reticulum (ER). Although it is well characterized in non-neuronal cells, a proliferation of papers over the past few years has revealed a key role for the UPR in normal neuronal function and as an important driver of neurodegenerative diseases. A complex scenario is emerging in which distinct UPR signalling modules have specific and even opposite effects on neurodegeneration depending on the disease context. Here, we provide an overview of the most recent findings addressing the biological relevance of ER stress in the nervous system.

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Equilibrated protein homeostasis (referred to as proteostasis) requires the dynamic coordination of efficient folding of newly synthesized proteins, quality control and degradative mechanisms to reduce the load of unfolded and/or misfolded proteins and thereby prevent abnormal protein aggregation[1]. Protein-folding networks consisting of cytoplasmic and endoplasmic reticulum (ER)-resident chaperones ensure proper folding of biologically active native proteins in a crowded cellular environment that can reach up to 300–400 grams per litre of proteins[2]. Quality control mechanisms recognize misfolded proteins and mediate their degradation by the proteasome, lysosome and macroautophagy pathways (BOX 1). Although cytoplasmic chaperones, such as the heat shock protein 70 (HSP70) system, are reasonably well understood, there is much less information on the function and regulation of ER folding and quality control mechanisms. Moreover, the hierarchical organization of the ER proteostasis network is poorly understood despite the discovery of dozens of factors participating in these processes.

Under conditions of cellular stress, such as rising levels of misfolded proteins, cells activate a dynamic signalling network known as the unfolded protein response (UPR), which aims to restore proteostasis. In addition to this physiological function, genetic manipulation of the pathway in animal models of disease has uncovered a fundamental contribution of the UPR to neurodegenerative conditions. A complex scenario is emerging in which distinct signalling modules of the UPR have specific and even opposite effects on neurodegeneration depending on the disease context. Sustaining cellular proteostasis becomes a greater challenge in diseases in which a mutant misfolded protein is expressed chronically throughout the life of an individual[3]. Attenuation of ER stress levels with pharmacological or gene therapy strategies has been successful in reducing pathological features in various animal models of neurodegeneration and thus holds promise as a therapeutic target for human neurodegenerative diseases. In this article, we provide an overview of the possible physiological functions of the UPR in the nervous system and discuss the most recent findings addressing the functional link between protein folding stress in the ER and neurodegeneration. We analyse in detail the mechanisms explaining how disease-related proteins affect the homeostasis of the ER. Last, the emerging impact of the ER stress signalling pathways on the physiology of the nervous system, cognition and ageing is also highlighted.

ER stress and UPR signalling

About one-third of the human proteome is synthesized in the ER and transits to membrane compartments such as the plasma membrane or undergoes secretion[3]. Several physiological and pathological conditions can alter the protein folding process at the ER, which leads to the accumulation of misfolded proteins in its lumen, a cellular state referred to as ER stress. For example, certain specialized secretory cells undergo physiological and non-lethal levels of ER stress owing to the high demand of protein folding and secretion, a phenomenon extensively described in B lymphocytes and pancreatic β-cells. By contrast, diverse pathological conditions can

Box 1 | **Proteostasis networks and protein aggregation**

Efficient protein folding and prevention of abnormal aggregation (proteotoxicity) in neurons relies on the proteostasis network, which provides a dynamic interconnection between cytoplasmic and endoplasmic reticulum (ER) quality control and folding mechanisms. When the protein folding capacity is saturated (such as with mutant proteins associated with neurodegenerative diseases), the proteasome and autophagy pathways act as a second barrier to degrade unfolded proteins and restore proteostasis. Under physiological conditions, most of the proteins transiting through the ER are properly folded, whereas in pathological situations there is an accumulation of misfolded proteins that can originate in the ER or cytoplasm. Misfolded proteins can accumulate within the ER owing to direct mutations in disease-related genes or perturbations in the function of the secretory pathway at different levels (FIG. 3). The load of misfolded protein in the ER is reduced by ER-associated protein degradation (ERAD), a process in which these proteins are targeted to the cytoplasm for proteasome-mediated degradation. If the proteasome is defective or saturated, or if there is an excess of reactive oxygen species in the cytoplasm, misfolded proteins tend to form toxic oligomers and larger aggregates that can then be eliminated by autophagy. Misfolded proteins can also accumulate in the cytoplasm and are folded by cytoplasmic chaperones, such as heat shock proteins. An overload of misfolded proteins in the cytoplasm can also saturate the proteasome and induce compensatory autophagy, inhibit ERAD function and promote ER stress. In several neurodegenerative diseases, proteasome activity and autophagy finally decline or are inhibited, which contributes to the increase in the overload of misfolded proteins, generating chronic ER stress and cell demise. A series of novel small molecules have been generated in the past few years to target ER proteostasis; these molecules have been shown to have proven efficacy in alleviating disease features in many preclinical models of disease[196].

trigger chronic stress that results in cell death, which can be initiated by alterations in the protein maturation process, ER calcium homeostasis, ER-to-Golgi vesicular trafficking, expression of mutant proteins and other events. In response to ER stress, the folding and degrading capacity of this organelle is dynamically adjusted by the induction of a complex signalling network known as the UPR. Whether UPR adaptive responses or pro-apoptotic programmes are triggered depends on the load of misfolded proteins and the temporality of the exposure to stress. Under moderate misfolded protein accumulation, activation of the UPR operates as a feedback mechanism that reinforces protein folding, quality control and protein degradation mechanisms[4–6] (FIG. 1). Abnormally folded proteins in the ER can be cleared out through the ER-associated protein degradation (ERAD) pathway, in which misfolded proteins are retrotranslocated to the cytosol, where they undergo ubiquitylation and proteasome-mediated degradation. In addition, UPR signalling enhances macroautophagy (from here on referred to as autophagy), which operates as an efficient mechanism to eliminate large protein aggregates and damaged organelles through the lysosomal pathway.

The UPR consists of two central components, a group of specialized stress sensors located at the ER membrane and downstream transcription factors that reprogramme gene expression to enable adaptation to stress or the induction of apoptosis. The UPR is mediated by three main signalling branches, including inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK) (FIG. 1). UPR activation induces a rapid and transient translational attenuation that is controlled by PERK through the direct phosphorylation and inhibition of the ubiquitous eukaryotic translation initiation factor 2α (eIF2α). This event efficiently buffers the load of misfolded proteins in the ER by reducing the entrance of newly synthesized proteins into its lumen. In addition to inhibiting global translation, eIF2α phosphorylation favours the selective translation of the mRNA encoding the transcription factor ATF4 (REF. 5). ATF4 controls the expression of various genes involved in apoptosis, autophagy, amino acid metabolism and antioxidant responses.

The most conserved UPR signalling branch, and the only one present in yeast, is initiated by IRE1. Dimerization of IRE1 and its autophosphorylation activate its endoribonuclease activity to catalyse the unconventional splicing of the mRNA encoding the transcription factor X-box binding protein 1 (XBP1). This event excises a 26-nucleotide intron that shifts the coding reading frame of the mRNA. Spliced XBP1 (XBP1s) is a stable and active transcription factor that controls a subset of UPR target genes related to protein folding, ERAD, protein translocation into the ER, lipid synthesis and other processes[7]. IRE1 also degrades a subset of specific mRNAs in a tissue-specific manner through regulated IRE1-dependent decay (RIDD) and activates alarm kinases, including the JUN amino-terminal kinase (JNK) and the apoptosis signal-regulating kinase 1 (ASK1) pathway, through the binding of adaptor proteins. ATF6 is a transcription factor that is anchored to the ER membrane in unstressed cells. Upon ER stress, ATF6 is cleaved by site 1 and 2 proteases at the Golgi apparatus, and the cytosolic ATF6 fragment translocates to the nucleus to activate the transcription of ERAD genes and *XBP1* (REF. 5). ATF6 can form heterodimers with XBP1 to control the induction of specific patterns of gene expression[8].

Under conditions of chronic or irreversible ER stress, the UPR induces apoptosis through distinct overlapping signalling mechanisms (FIG. 1), which include the upregulation of the transcription factor C/EBP-homologous protein (CHOP) and its target growth arrest and DNA damage-inducible 34 (GADD34; also known as PPP1R15A), in addition to pro-apoptotic components of the BCL-2 protein family. Most studies have linked the induction of downstream PERK signalling events to the induction of cell death. In particular, sustained activation of PERK triggers a series of successive transcriptional responses mediated by ATF4 and downstream upregulation of CHOP, which in turn can inhibit the expression of survival protein BCL-2 and engage pro-apoptotic proteins such as Bcl2-interacting mediator of cell death (BIM) and p53 upregulated modulator of apoptosis (PUMA; also known as BBC3) (FIG. 2). This cascade of events results in the activation of BAX- and BAK-dependent apoptosis at the mitochondria and the activation of the caspase cascade[9]. Several additional pathways have also been proposed to induce apoptosis under chronic ER stress, including calcium signalling, microRNAs and mitogen-activated protein kinases (FIG. 2) (reviewed in REFS 10–12). Interestingly, a recent study has shown that ATF4 and CHOP trigger apoptosis not only by regulating BAX- and BAK-dependent mechanisms but also by increasing protein synthesis within stressed cells. This phenomenon results in ATP depletion,

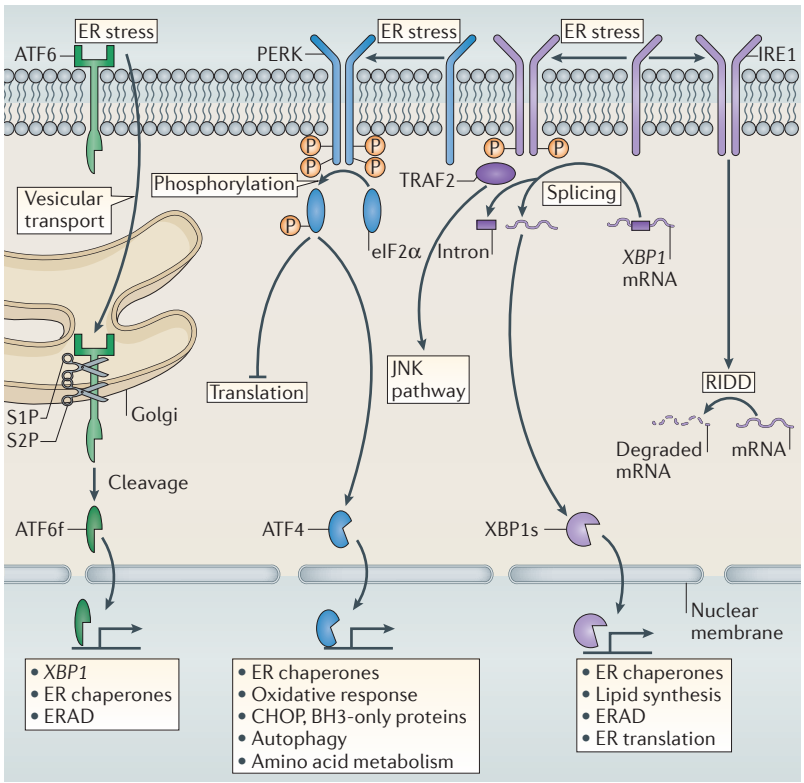

Figure 1 | **UPR signalling pathways in mammals.** Accumulation of misfolded proteins in the endoplasmic reticulum (ER) activates the unfolded protein response (UPR) sensors inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK). Upon ER stress, ATF6 is transported to the Golgi, where it is cleaved by site 1 protease (S1P) and S2P, releasing the cytosolic ATF6 fragment (ATF6f), which operates as a transcription factor. ATF6f induces genes required for ER-associated protein degradation (ERAD) and modulates X-box binding protein 1 (*XBP1*) mRNA levels. ER stress also activates PERK, which phosphorylates eukaryotic translation initiation factor 2α (eIF2α). This results in the inhibition of protein translation, except that of *ATF4* mRNA. After translocation to the nucleus, ATF4 induces the expression of ER chaperones, genes related to autophagy, redox control and amino acid metabolism. ATF4 also controls genes related to apoptosis, including C/EBP-homologous protein (*CHOP*). Active IRE1 induces the splicing of mRNA encoding XBP1, leading to the expression of an active transcription factor XBP1s that upregulates ER chaperones, genes involved in the ERAD pathway and genes that regulate lipid synthesis. IRE1 also signals through XBP1-independent pathways. IRE1 associates with tumour necrosis factor (TNF) receptor-associated factor 2 (TRAF2) and induces JUN amino-terminal kinase (JNK) activation and thereby modulates autophagy and apoptosis. IRE1 endoribonuclease activity also induces a process known as regulated IRE1-dependent mRNA decay (RIDD) that affects different pathways, including those involved in lipid biosynthesis and apoptosis.

oxidative stress and cell death by 'poisoning' damaged cells with misfolded proteins[13]. By contrast, it is important to highlight that in many experimental settings, eIF2α phosphorylation promotes a strong pro-survival effect[14]. Although less explored, several reports indicate that the IRE1 pathway also contributes to apoptosis. For example, downstream activation of the JNK[15] and ASK1 pathway triggers apoptosis under ER stress conditions. Similarly, RIDD activity can induce cell death by degrading mRNA that encodes essential ER chaperones and by the downregulation of microRNAs that negatively regulate the expression of pro-apoptotic caspases (reviewed in REF. 12).

In summary, the UPR constitutes a complex signalling network that orchestrates adaptation to ER stress or the elimination of damaged cells by integrating information about the intensity and duration of the stress stimuli (FIG. 2). In the context of neurodegenerative diseases, this dual aspect of UPR signalling makes it difficult to predict the precise contribution of the pathway to pathological conditions, and elucidating this issue has required extensive functional studies *in vivo* (see next sections).

Protein misfolding and neurodegeneration

The identification of curative therapies for neurodegenerative diseases remains one of the biggest challenges in neuroscience. This need is becoming even more pressing, as increased life expectancy and the concurrent rise in neurodegenerative pathologies become a large health and economic burden. Neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and prion-related diseases (PrDs), have different clinical manifestations, but all involve the accumulation of misfolded pathological proteins and are now classified as protein misfolding disorders (PMDs)[16]. For example, AD is characterized by cognitive alterations, memory loss and behavioural changes. Amyloid plaques and neurofibrillary tangles are the hallmark lesions in the pathology and both arise from protein misfolding. The plaques are mainly composed of amyloid-β peptides of 40–42 amino acids that are produced from the cleavage of the amyloid precursor protein (APP) by secretases, whereas neurofibrillary tangles are composed of the aberrantly phosphorylated tau protein[17,18]. PD involves decreased movement control and is characterized by the appearance of several motor symptoms due to the loss of dopaminergic neurons in the substantia nigra pars compacta. Lewy bodies are distinct protein inclusions that are found in PD and are composed of aggregated α-synuclein[19,20]. ALS is a progressive paralytic disease, involving the selective degeneration of motor neurons in the spinal ventral horn, most of the brainstem and the cerebral cortex. Many different mutations associated with familial ALS lead to protein misfolding and aggregation; these mutations can affect the genes encoding superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 KDa (TDP43), fused in sarcoma (FUS; also known as TLS) and other proteins[21]. HD is a late-onset autosomal dominant neurodegenerative disease, involving the accumulation large-protein inclusions generated by mutant huntingtin protein owing to an expansion of a polyglutamine region[22]. Finally, Creutzfeldt–Jakob disease (CJD), the most common form of PrD, is characterized by the spongiform degeneration of the brain accompanied by the accumulation of a misfolded and protease-resistant form of the prion protein (PrP)[23]. Thus, even though the clinical manifestation of all these diseases is diverse, at the molecular level they share the phenomenon of accumulation of abnormally folded proteins in the form of small oligomers, aggregates or large-protein inclusions.

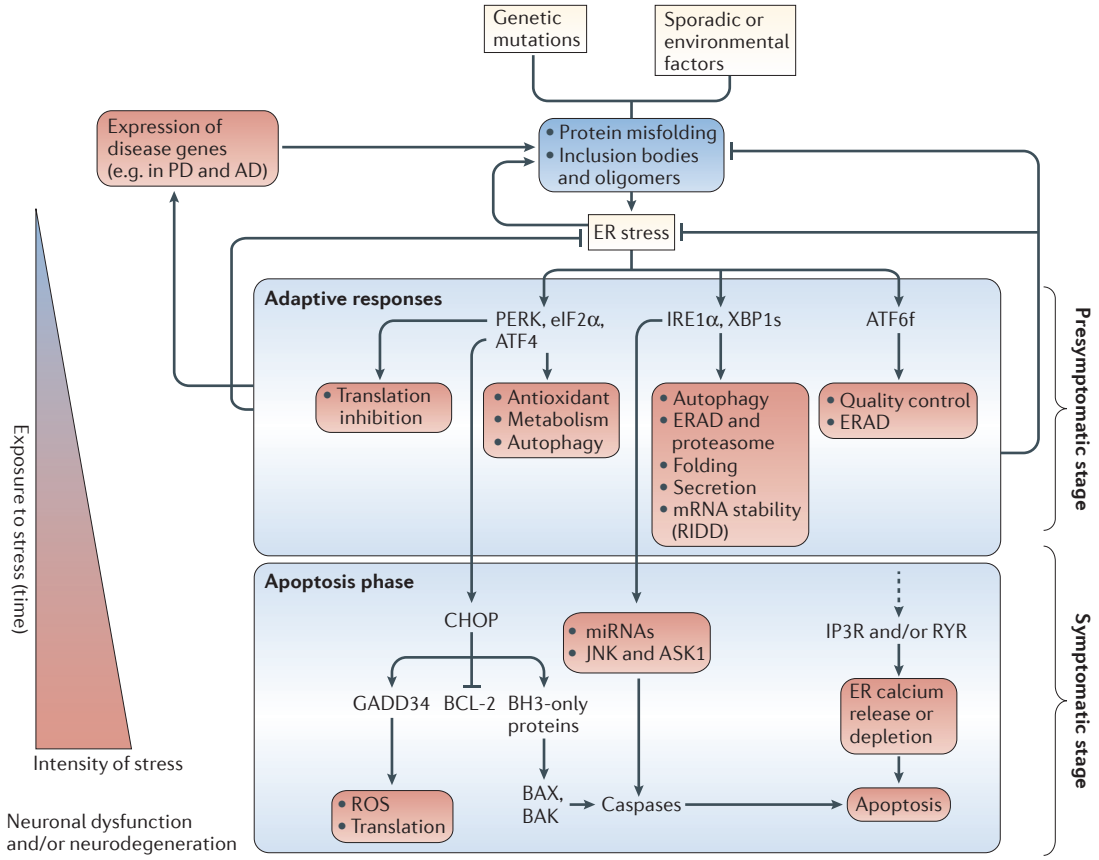

Figure 2 | **UPR signalling outputs and neurodegeneration.** Environmental factors and certain mutations in specific disease-related genes can trigger the misfolding of a particular protein, which can then form different types of aggregates, ranging from small oligomeric species to inclusion bodies. This abnormal aggregation process affects the function of the endoplasmic reticulum (ER) at different levels, resulting in ER stress. ER stress may further increase aggregation of disease-related proteins through a feedback loop by altering the folding and quality control capacity of the cell or by modifying the expression of disease-related genes. ER stress engages the unfolded protein response (UPR) sensors, which in turn activate distinct downstream responses. Early UPR signalling events attenuate protein synthesis at the ER by transiently inhibiting translation and by enhancing regulated inositol-requiring enzyme 1 (IRE1)-dependent mRNA decay (RIDD) and autophagy. In addition, other UPR adaptive responses are triggered through transcriptional control (mediated by protein kinase RNA-like ER kinase (PERK), eukaryotic translation initiation factor 2α (eIF2α), spliced X-box binding protein 1 (XBP1s), activating transcription factor 6 fragment (ATF6f) and ATF4), upregulation of genes involved in ER-associated protein degradation (ERAD), folding and quality control mechanisms. Prolonged ER stress overcomes the adaptive responses of the UPR and apoptosis is induced. Various apoptotic pathways have been described, including upregulation of C/EBP-homologous protein (CHOP) through ATF4. This pathway also inhibits the expression of BCL-2 family members, and the upregulation of BH3-only proteins results in BAK- and BAX-dependent apoptosis. CHOP also induces the expression of growth arrest and DNA damage-inducible 34 (GADD34), which increases the levels of reactive oxygen species (ROS) and increases protein synthesis. Altered calcium homeostasis due to inositol trisphosphate receptor (IP3R) or ryanodine receptor (RYR) activation (by an unknown mechanism, indicated by dashed arrow) may also contribute to cell death. IRE1α also induces the activation of JUN amino-terminal kinase (JNK) and apoptosis signal-regulating kinase 1 (ASK1), which contributes to cell death. In addition, IRE1α can degrade microRNAs (miRNAs) that negatively control the expression of caspases. UPR signalling events also can modulate the expression of various genes involved in the aetiology of the disease. AD, Alzheimer's disease; PD, Parkinson's disease. Figure is modified, with permission, from REF. 4 © (2012) Macmillan Publishers Ltd. All rights reserved.

Although, the molecular mechanisms underlying PMDs remain largely obscure, over the past few years, it has been found that disturbance of several aspects of the proteostasis network contributes to the progression of these neurodegenerative diseases[24]. Moreover, the impact of ER stress on the progression of neurodegenerative diseases is starting to be elucidated. Many correlative studies in human post-mortem tissue have shown that the presence of UPR markers in the brain is temporally and spatially associated with abnormal protein aggregation and the occurrence of neuropathological features[25] (TABLE 1). In agreement with these findings, a close association has been proposed between the occurrence of neurodegeneration and the upregulation of ER stress markers in animal models of AD, PD, ALS, HD and PrD (see specialized

Table 1 | **ER stress in neurodegenerative diseases**

Disease	Protein	Observation	Refs
Alzheimer's disease	Phosphorylated tau	Neurons expressing phosphorylated tau activate the UPR, including PERK signalling	197
	Amyloid-β	PDI family members are upregulated and colocalize with protein aggregates	198
		A polymorphism on the *XBP1* promoter is a risk factor for Alzheimer's disease	125
		XBP1s is downregulated in Alzheimer's disease brains	199
Frontotemporal dementia	Tau	Tau mutations trigger ER stress	200
Parkinson's disease	α-synuclein	Dopaminergic neurons containing Lewy bodies develop signs of ER stress, including phosphorylation of PERK	201–203
ALS	Sporadic cases	Spinal cord tissue from sporadic ALS cases shows global markers of ER stress, including XBP1 and ATF4	31,46,204–206
		ERp57 and PDI have been identified as possible biomarkers of ALS in human blood	30
		PDI is upregulated in CSF from patients with ALS	31
		PDI intronic genetic variants are a risk factor for ALS	127
Huntington's disease	Huntingtin	XBP1s is upregulated in the striatum of patients	47
Creutzfeldt–Jakob disease	Prion protein	ER stress markers, including ERp57, are upregulated in the cerebellum and cortex	52,95,207,208

A summary is presented of the most relevant findings correlating the occurrence of endoplasmic reticulum (ER) stress with neurodegenerative diseases based on the analysis of human post-mortem tissue. Activation of proximal unfolded protein response (UPR) events is also highlighted. ALS, amyotrophic lateral sclerosis; ATF4, activating transcription factor 4; CSF, cerebrospinal fluid; ERp57, ER resident protein 57; PDI, protein disulphide isomerase; PERK, protein kinase RNA-like ER kinase; XBP1, X-box binding protein 1; XBP1s, spliced XBP1.

reviews in REFS 26–29). In diseases such as ALS, the detection of ER stress markers in body fluids has even been suggested as a reliable approach to follow disease progression[30,31] (TABLE 1). From these correlative studies, the concept has emerged that ER stress is a deleterious process contributing to neurodegeneration. However, on the basis of functional studies in mouse models (see next section), it is becoming clear that the scenario is very complex, and in some diseases the engagement of specific UPR signalling events may actually operate as a beneficial reaction to maintain proteostasis.

Impact of the UPR on neurodegeneration

The idea that ER stress contributes to neurodegeneration has been around for more than a decade. The initial prediction was that activation of the UPR contributed to neuronal loss by activation of a pro-apoptotic stress signal. However, more recent and extensive studies using genetic and pharmacological manipulation of key UPR components have uncovered an unexpected scenario. UPR activation can either enhance or reduce neurodegeneration — and sometimes may even have opposite effects on disease progression — depending on which specific UPR signalling mechanisms are activated (FIG. 2). In this section, we summarize the most relevant data supporting this interesting concept — that is, that the consequences and/or outputs of the UPR in neurodegenerative conditions can depend on the specific nature of the pathological input (TABLE 2). For simplicity, these diseases are discussed in three main groups.

Protein misfolding disorders. Studies addressing the impact of ER stress on PD have consistently indicated that chronic ER stress is a pathological event that contributes to the degeneration of dopaminergic neurons of the substantia nigra. ER stress was recently identified as a salient feature of neuronal cultures generated from induced pluripotent stem cells obtained from patients with PD[32]. For example, ablation of components of the UPR mediating adaptation to stress, such as ATF6, enhances the susceptibility of mice to PD-inducing neurotoxins[33,34], whereas overexpression of binding immunoglobulin protein (BiP; also known as GRP78)[35] or treatment of α-synuclein transgenic mice with salubrinal[36] (an inducer of eIF2α phosphorylation[37]) leads to neuroprotection. These effects are similar to those described in *Chop*-deficient animals[38].

However, the scenario in HD and ALS is more complex. Most studies assessing the impact of ER stress on ALS have been carried out in mutant SOD1 mice, which only represent 2% of total cases. Gene expression profile analysis of vulnerable and resistant motor neurons in ALS mouse models indicated that chronic ER stress is the earliest pathological event detected that selectively occurs in vulnerable neurons during the pre-symptomatic stage of the disease[39]. Targeting the PERK signalling branch in this ALS model revealed a bifunctional role of the pathway in the disease, in which eIF2α phosphorylation had a protective effect, possibly due to a reduction in the load of unfolded proteins in the ER[39,40], but expression of ATF4 had detrimental consequences associated with the upregulation of pro-apoptotic components such as *Chop*

Table 2 | **Functional impact of distinct UPR signalling components in brain diseases**

Disease	Model	UPR manipulation	Phenotype	Refs
Amyotrophic lateral sclerosis	Mutant SOD1 Tg mice	PERK heterozygous	Disease exacerbation, increased SOD1 aggregation	40
		Salubrinal	Extended lifespan	39
		ATF4 knockout	Partial embryonic lethality, protection against disease progression	41
		XBP1 CNS-specific knockout	Neuroprotection, extended lifespan, decreased SOD1 aggregation	46
Parkinson's disease	α-synuclein Tg mice	Salubrinal	Neuroprotection	36
	Neurotoxins	AV XBP1s	Increased dopaminergic neuron survival	209
		ATF6 knockout	Increased neurodegeneration	33,34
		CHOP knockout	Neuroprotection	38
		AAV BiP	Dopaminergic neuron survival, decreased α-synuclein aggregation	35
Huntington's disease	Mutant HTT Tg mice	ATF4 knockout	No effects on mutant HTT aggregation	47
		XBP1 CNS-specific knockout	Neuroprotection, improved motor performance, reduced HTT levels	47
		AAV XBP1s	Decreased mutant HTT aggregation	210
Prion-related diseases	Scrapie prion	Salubrinal	Disease exacerbation	55
		XBP1 CNS-specific knockout	No effects on disease progression or prion replication	53
		Caspase 12 knockout	No effect on disease progression or prion replication	54
		LV GADD34	Global neuroprotection	55
		PERK inhibitor	Reduced neurodegeneration, delayed disease progression	56
Spinal cord injury	Mechanical injury	Salubrinal	Improved motor recovery and oligodendrocyte survival	67,211
		ATF4 knockout	Reduced motor recovery, increased oligodendrocyte apoptosis	66
		XBP1 CNS-specific knockout	Reduced locomotor recovery	66
		CHOP knockout	Increased locomotor recovery and oligodendrocyte survival	68,69
		AAV XBP1s	Improved motor recovery and oligodendrocyte survival	66
Alzheimer's disease	APP/PS1 Tg mice	JNK3 knockout	Reduced amyloid-β, neuronal loss and cognitive dysfunction	59
		PERK CNS-specific knockout	Improved learning, memory and LTP	61
Multiple sclerosis	EAE	PERK heterozygous	Increased pathology, reduced oligodendrocyte survival	79
		PERK-inducible Tg rodent	Global neuroprotection	81
		Salubrinal	Decreased axonal degeneration, improved motor performance	80
		GADD34 knockout	Global neuroprotection	78
Charcot–Marie–Tooth disease	Mutant peripheral myelin	Salubrinal	Neuroprotection, increased Schwann cell survival and motor recovery	83
		CHOP knockout	Global neuroprotection	84
		GADD34 knockout	Global neuroprotection	84
Pelizaeus–Merzbacher disease	Mutant proteolipid protein	CHOP knockout	Disease exacerbation, increased oligodendrocyte apoptosis	82
Retinitis pigmentosa	Mutant rhodopsin	AAV BiP	Neuroprotection, restored vision	65
		CHOP knockout	No effects	212
Optic nerve degeneration	Nerve crush	CHOP knockout	Increased retinal ganglion cell survival	71
		XBP1 CNS-specific knockout	No effects	71
		AAV XBP1s	Increased retinal ganglion cell survival	71
Brain ischaemia	MCAO	BIX	Decreased infarct volume	73

A summary of selected studies depicting differential effects of manipulating specific unfolded protein response (UPR) signalling modules in preclinical models of neurodegeneration. AAV, adeno-associated virus; ATF, activating transcription factor; AV, adenovirus; BiP, binding immunoglobulin protein; BIX, BiP inducer X; CHOP, C/EBP-homologous protein; EAE, experimental autoimmune encephalomyelitis; GADD34, growth arrest and DNA damage-inducible 34; HTT, huntingtin; JNK3, JUN amino-terminal kinase 3; LTP, long-term potentiation; LV, lentivirus; MCAO, middle cerebral artery occlusion; PERK, protein kinase RNA-like ER kinase; SOD1, superoxide dismutase 1; Tg, transgenic; XBP1s, spliced X-box binding protein 1.

and *Bim*[41]. Consistent with this idea, ablation of PUMA, BIM or ASK1 expression provides protection against experimental ALS[42–44]. This concept was reinforced in a recent study using zebrafish and *Caenorhabditis elegans* models expressing mutant TDP43, in which the pharmacological induction of eIF2α phosphorylation reduced neurodegeneration[45]. In contrast with the findings of this study, targeting XBP1 in the nervous system provided protection against ALS[46]. These unexpected effects were explained by a possible switch in the protein homeostasis network towards the upregulation of autophagy levels, which mediated the degradation of mutant SOD1 aggregates[46]. Virtually identical results have been described for a transgenic mouse model of HD in which XBP1 was knocked out[47]. The neuroprotective effects observed in these mice were proposed to be caused by the induction of autophagy through the upregulation of the transcription factor forkhead box O1 (FOXO1), an important regulator of autophagy and ageing-related processes[47,48]. In contrast to ALS, in HD ATF4 deficiency did not affect mutant huntingtin levels[47].

Although infectious PrDs are extremely rare diseases, they are becoming an attractive model to investigate the emerging self-propagating properties of protein misfolding in neurodegenerative diseases, a common feature of AD, PD and ALS[49,50]. A recent study in models of PrD discovered an unpredicted pathological mechanism that involves deregulated UPR signalling. Although ER stress has been extensively described in models of infectious forms of PrD[51,52], its contribution to prion pathogenesis has been questioned because disease progression and pathophysiology are unaffected by *Xbp1* or caspase 12 (an ER-resident caspase) deficiency[53,54]. By contrast, a recent report indicated that prion replication leads to sustained eIF2α phosphorylation, which represses the translation of a cluster of synaptic proteins that are synthesized through the ER–Golgi secretory pathway[55]. This event was responsible for the neurological and behavioural impairment in experimental PrD[55]. In agreement with these findings, oral administration of a PERK inhibitor prevented translational repression and thus protected animals from PrD-related neurodegeneration[56]. These interesting studies suggest that depending on the disease context, translational repression by the PERK–eIF2α signalling branch may have contrasting and unpredicted effects on disease progression.

Although AD is one of the most common neurodegenerative diseases, studies evaluating the impact of the UPR on AD *in vivo* are surprisingly minimal, and most of the studies that are available are based on correlative associations or cell culture experiments (reviewed in REF. 57). Using an AD model in *Drosophila melanogaster*, the enforced expression of active Xbp1 was shown to protect against amyloid-β toxicity, possibly through reduced release of calcium from the ER[58]. A recent report proposed an interesting model depicting a vicious 'stress cycle' in which ER stress affects the generation of amyloid-β. Specifically, the report suggested that the activation of JNK3 by ER stress in models of AD increased amyloid-β production, amplifying the ER stress response[59]. Similar to the phenotypes described for HD and AD in animals in which *Xbp1* was knocked out, a recent study in *C. elegans* indicated that targeting XBP-1 protects against amyloid-β toxicity and that this protective effect correlated with enhanced autophagy and augmented stress levels[60]. Remarkably, in a recent study using genetic models of AD, the observed memory impairment was reversed by ablation of PERK expression in the brain[61]. By contrast, another recent study proposed that phosphorylation of eIF2α in AD actually occurs through RNA-activated protein kinase (PKR; also known as eIF2αK2) and not PERK[62].

Finally, another disease that we highlight in this section is retinitis pigmentosa, which is a degenerative eye disease that involves loss of photoreceptors and is often caused by mutant misfolded rhodopsin protein. Several studies in fly models have demonstrated that ER stress signalling operates as both a survival and a pathological mechanism in retinal degeneration. In the fly retinitis pigmentosa model, misfolded mutant Rhodopsin 1 ($Rh1^{mut}$) proteins accumulate in the ER, which triggers the UPR. Under normal light conditions, misfolded $Rh1^{mut}$ generates mild ER stress (non-toxic) that preconditions the system towards activation of the adaptive UPR (see also hormesis section below)[63]. By contrast, under constant exposure to bright light, misfolded $Rh1^{mut}$ induces toxic ER stress that is accelerated by Xbp1 haploinsufficiency[64]. Finally, an elegant study using a transgenic rat model of retinitis pigmentosa demonstrated that the subretinal delivery of a BiP-based gene therapy restored visual function[65], providing a proof of concept for the impact of alleviating ER stress in this disease.

In conclusion, these studies suggest that predicting the contribution of the UPR to neurodegenerative diseases is complex and non-linear, possibly owing to the pleiotropic effects of ER stress signalling and the cross-talk with other important stress responses involved in neuroprotection, such as autophagy (FIG. 2). All of the data discussed here highlight the need for a systematic assessment of the contribution of specific UPR signalling branches to distinct neurodegenerative diseases.

Mechanical injury and ischaemia-reperfusion. Spinal cord injury (SCI) is one of the major causes of paralysis and involves the mechanical damage of axons. Functional studies in several animal models of SCI indicate that the UPR has an important role in counteracting cellular stress, possibly by affecting the function and survival of oligodendrocytes. *Xbp1* mRNA splicing and ATF4 expression are upregulated very early after mild to moderate SCI, and this has positive effects on the partial locomotor recovery achieved after a traumatic event[66,67]. Moreover, gene therapy to deliver XBP1s into the damaged area after SCI improved locomotor recovery[66]. In agreement with this, a late chronic ER stress response also contributes to neuronal dysfunction and oligodendrocyte death, as shown by increased functional recovery of *Chop*-deficient mice in models of mild SCI[68,69]. These protective effects are not observed in models of severe SCI[70]. A similar mechanism was proposed for experiments involving optic nerve damage by crushing, chemotherapy or glaucoma[71].

The upregulation of ER stress markers has been extensively described in models of brain and spinal cord ischaemia-reperfusion. However, there are few functional data uncovering the biological meaning of ER stress in this pathological condition. Treatment with salubrinal can protect the hippocampus against excitotoxicity, a known pathological component of the damage incurred in brain ischaemia-reperfusion models[72]. In addition, a small molecule known as BIX induces *Bip* expression and exerts protective effects against cerebral ischaemia[73]. Chemical chaperones, which are small molecules that stabilize protein conformation[74], also have protective effects in models of brain ischaemia that correlate with reduced levels of ER stress (see examples in REFS 75,76).

Myelin and lipid storage disorders. Oligodendrocytes and Schwann cells produce high amounts of plasma membrane during the myelinating process, making them highly susceptible to perturbations in ER function (reviewed in REF. 77). The most common myelin-related disorder is multiple sclerosis. Several reports have shown that chronic ER stress partly mediates the loss of oligodendrocytes in experimental models of multiple sclerosis. For example, early studies showed that in various multiple sclerosis models, activation of PERK contributes to oligodendrocyte survival and remyelination (see examples in REFS 78–80). Remarkably, an elegant study recently demonstrated that persistent artificial activation of PERK in oligodendrocytes does not trigger apoptosis, attenuates the development of experimental multiple sclerosis and is associated with improved remyelination, oligodendrocyte survival and axonal degeneration[81]. ER stress has also been linked to oligodendrocyte survival in other myelin-related disorders. For example, in Pelizaeus–Merzbacher disease, a mutation in the gene encoding the proteolipid protein, the main constituent of myelin, leads to its retention in the ER. Surprisingly, *Chop*-null animals showed an exacerbated disease phenotype and an increased loss of oligodendrocytes through an unknown mechanism[82].

Schwann cells are also highly susceptible to ER stress, as has been shown in models of Charcot–Marie–Tooth disease, which is triggered by mutations in genes encoding peripheral myelin components. Functional studies have demonstrated that translational control and CHOP expression are crucial factors involved in the disease, as an almost complete rescue of the disease phenotype is observed in CHOP- or GADD34-deficient mice or after treatment with salubrinal[83,84]. Other areas of research, such as the study of Wallerian degeneration of peripheral nerves, which is a common side effect of treatments, such as chemotherapy, remain to be explored in the context of the UPR.

Recent evidence indicates that the UPR has an important role in fine-tuning cholesterol and lipid metabolism in the body[85,86]. Lysosomal storage disorders are a group of fatal neurodegenerative and hereditary conditions associated with lysosomal dysfunction[87]. One of these diseases, Niemann–Pick type C disease, is a sphingolipid storage disorder that results from inherited deficiencies in intracellular lipid-trafficking proteins and is characterized by an abnormal intracellular accumulation of cholesterol and glycosphingolipids. Similarly, GM1 gangliosidosis and infantile neuronal ceroid lipofuscinoses involve abnormal sphingolipid metabolism. These lysosomal storage disorders have been shown to be associated with the occurrence of chronic ER stress in several studies[88–91]. However, functional data linking cholesterol and sphingolipid alterations to the UPR in the brain are still lacking, and this topic remains an interesting area for future research.

As the examples discussed above make clear, there has been an explosion of functional studies in recent years that validate the UPR signalling network as a relevant target for future therapeutic strategies (TABLE 2). These therapies could be used to treat not only classical PMDs but also other pathological conditions, such as mechanical brain injury, stroke, axonal degeneration and autoimmune diseases.

What causes ER stress in neurodegeneration?

As discussed above, protein misfolding is a common feature of several neurodegenerative diseases. However, the cellular responses triggered by this pathological perturbation can vary depending on the nature of the protein affected and its subcellular distribution. Indeed, a number of ground-breaking studies demonstrated that ER stress is a crucial component underlying neuronal loss in cellular models of AD[92–94]. But is ER stress a response to neurodegeneration or does it contribute to disease initiation? Although most initial studies have placed the pathway as a downstream pathological event driving degeneration, recent evidence suggests that perturbations of the UPR may be part of the aetiology of several diseases. It is also important to highlight the fact that only few examples indicate a direct alteration of ER function by disease-related proteins. In general, the induction of ER stress in neurodegenerative diseases is indirect, which is in agreement with the finding that many PMD-related proteins are not located in the ER lumen or its membrane but in the cytoplasm. In this section, we provide an overview of different mechanisms that have been proposed to explain the molecular link between neurodegeneration and the induction of ER stress (see molecular details in FIG. 3).

Interactions with the folding machinery. The accumulation of disease-related misfolded proteins inside the ER has been reported in a subgroup of neurodegenerative conditions. A few examples have shown that mutations in neurodegenerative diseases affect proteins that are synthesized through the secretory pathway, leading to their retention in the ER lumen and their degradation by the ERAD pathway. This is the case, for example, for mutant ATP13A2 (also known as PARK9) in PD, mutant PrP in familial CJD and mutant rhodopsin. The accumulation of these mutant proteins in the ER triggers a chronic ER stress response[95–97], but as mentioned above, there is no evidence so far that they engage the activation of UPR stress sensors directly as a 'danger signal'.

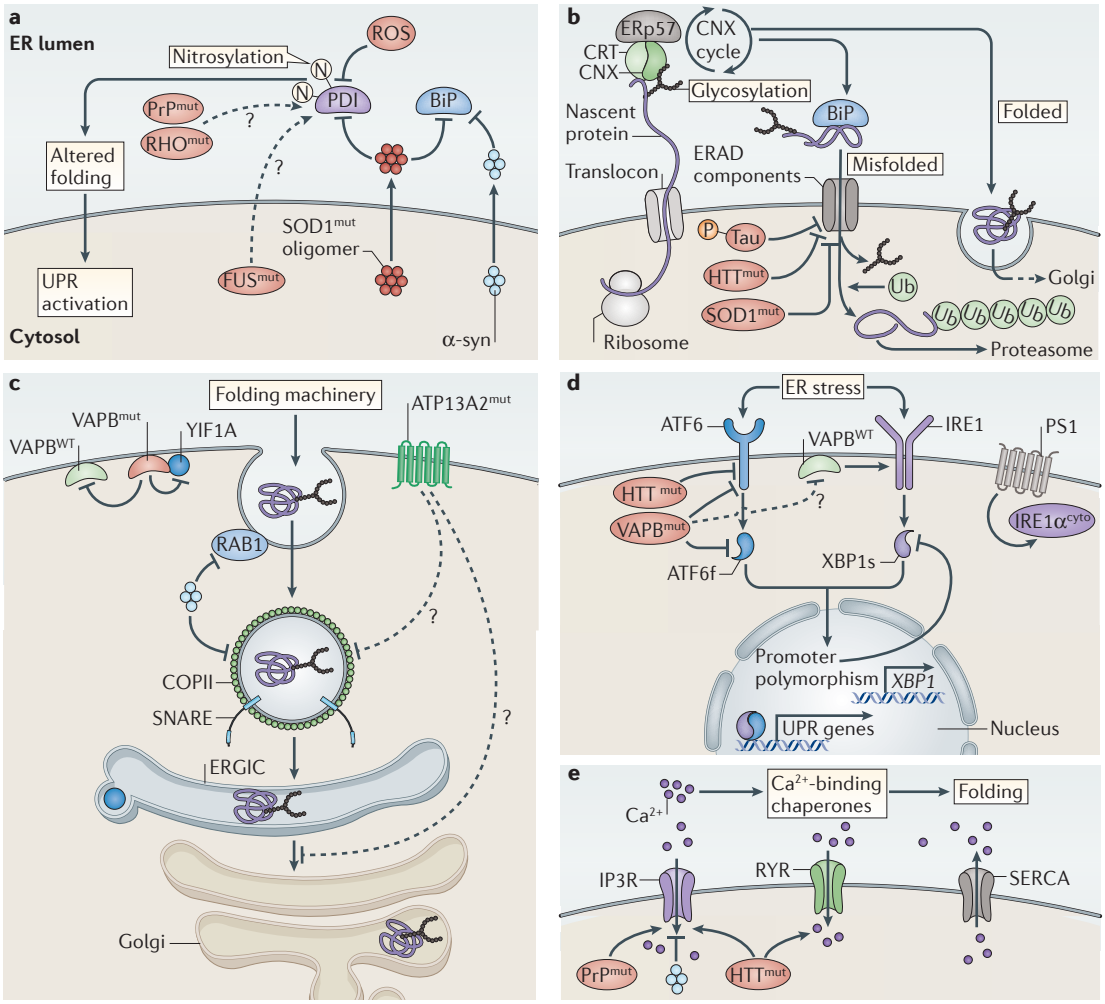

Figure 3 | **Disturbance of ER homeostasis in neurodegenerative diseases.** Properly folded proteins are processed in the endoplasmic reticulum (ER) and then traffic to the Golgi apparatus for further maturation and distribution to their final destination. This secretory process is altered in many neurodegenerative diseases. **a** | Mutant rhodopsin (RHO^{mut}) or infectious misfolded prion protein (PrP^{mut}) accumulate in the ER, interfere with the folding machinery (protein disulphide isomerase (PDI)) and induce the unfolded protein response (UPR). α-synuclein (α-syn) oligomers are found within the ER, where they interact with binding immunoglobulin protein (BiP). Similarly, mutant superoxide dismutase 1 ($SOD1^{mut}$) oligomers are found in the ER lumen and bind to PDI and BiP. Mutant fused in sarcoma (FUS^{mut}) also associates with PDI. These interactions may result in the sequestration of these chaperones, ablating their function. PDI can also be inactivated during oxidative stress (reactive oxygen species (ROS) production) via nitrosylation of their active site. **b** | Upon post-translational translocation to the ER, nascent proteins are glycosylated and then folded through the calnexin (CNX) and calreticulin (CRT) cycle, which involves ER resident protein 57 (ERp57; also known as PDIA3). Properly folded glycoproteins traffic through the ER to the Golgi, whereas abnormally folded proteins are retrotranslocated back to the cytosol, a process mediated by ER-associated protein degradation (ERAD) protein complexes, where they are deglycosylated and ubiquitylated for degradation by the proteasome. Mutant huntingtin (HTT^{mut}), $SOD1^{mut}$ or phosphorylated tau proteins interact with ERAD components, resulting in its inhibition, which in turn causes ER stress. **c** | α-syn interacts with RAB1 to inhibit the exit of vesicles from the ER, to the ER–Golgi intermediate compartment (ERGIC) and on to the Golgi, by associating with SNAREs. Similarly, ATP13A2 inhibits vesicular traffic and membrane fusion between the ER and Golgi. Mutant vesicle-associated membrane protein-associated protein B ($VAPB^{mut}$) sequesters YIF1A and wild-type VAPB ($VAPB^{WT}$), both of which are required for trafficking. All of these pathological events may ablate the maturation of proteins at the Golgi, triggering ER stress. **d** | A polymorphism on the X-box binding protein 1 (*XBP1*) promoter reduces *XBP1* transcription levels and is associated with Alzheimer's disease and bipolar disorders. $VAPB^{WT}$ enhances the activation of inositol-requiring enzyme 1 (IRE1), whereas $VAPB^{mut}$ antagonizes it, possibly owing to a physical interaction with $VAPB^{WT}$. $VAPB^{mut}$ also inhibits the transcriptional activity of activating transcription factor 6 (ATF6) through direct interaction and thus inhibits the expression of UPR target genes. Presenilin 1 (PS1) may interfere with ER stress signalling by promoting abnormal processing of IRE1, which results in the release of its cytosolic domain ($IRE1\alpha^{cyto}$). **e** | Calcium homeostasis is maintained in the ER by the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) pump that enables calcium to enter the ER. In addition, ryanodine receptors (RYRs) and inositol trisphosphate receptors (IP3Rs) promote calcium efflux. HTT^{mut} or PrP^{mut} enhance calcium release possibly by interacting with IP3R and RYR. α-syn can also inhibit IP3R function. Dashed arrows indicate that the mechanism is uncertain. ATF6f, ATF6 fragment; XBP1s, spliced XBP1.

Recent reports indicate that α-synuclein oligomers are present inside the ER in animal models of α-synucleopathies and in human post-mortem tissue from patients with PD[36,98]. Moreover, α-synuclein was reported to interact with essential ER chaperones such as BiP[98,99]. This led the authors to speculate that α-synuclein oligomers may sequester components of the ER folding machinery, triggering a chronic disturbance of ER proteostasis (FIG. 3a). Similar observations have been reported for mutant SOD1 in ALS models. Although SOD1 does not have an evident ER signal peptide, it can translocate to the ER[100–102], and it is even secreted through a classical mechanism involving the Golgi compartment[103,104]. Mutant SOD1 aggregates are observed in association with the ER foldases BiP and protein disulphide isomerase (PDI), which catalyses the formation of disulphide bonds at the ER, in microsomal fractions of spinal cord derived from mouse models of ALS[100,101]. Similarly, mutant FUS and TDP43 were recently reported to associate with PDI in cell culture models and ALS human post-mortem tissue[105,106]. Wild-type and misfolded PrP can also physically interact with PDIs[51,107]. Functional studies in cell culture models suggest that these ER chaperones may actually reduce protein aggregation and increase neuronal viability, possibly owing to a reduction of general ER stress[51,100,108]. In addition, direct inactivation of PDI through oxidative modification (nitrosylation), which may ablate the neuroprotective activity of this foldase, has been suggested in models of PD, AD[109] and ALS[108]. By contrast, drug screening to identify compounds that block amyloid-β and mutant huntingtin toxicity revealed that PDIs might actually contribute to the activation of apoptosis[110].

ERAD and protein trafficking impairment. There is accumulating evidence that abnormal protein–protein interactions could cause distinct perturbations in the secretory pathway in PMDs, in turn generating chronic ER stress. For example, mutant SOD1 and huntingtin have been shown to target the ERAD machinery, leading to ERAD impairment and pathological ER stress[44,111,112] (FIG. 3b). This mechanism was also recently reported for phosphorylated tau in AD models[113]. Another mechanism that generates a global alteration in ER proteostasis is the inhibition of factors involved in ER-to-Golgi trafficking and membrane fission and fusion, such as the ER exit factor RAB1 and SNAREs, as reported for α-synuclein[114–117] (FIG. 3c). Similarly, an interactome screening identified ATP13A2-binding partners that are involved in ER-to-Golgi vesicular trafficking and membrane fusion, in addition to the ER translocation machinery[118]. ALS-linked mutant vesicle-associated membrane protein-associated protein B (VAPB) accumulates in the ER and has recently been shown to sequester YIF1A, a protein located in the ER–Golgi intermediate compartment (ERGIC) that participates in vesicle trafficking in the secretory pathway[119]. VAPB expression also modulates the localization of ER quality control components, a function that is lost in ALS-linked mutant VAPB[120]. In models of HD, mutant huntingtin can also alter the trafficking through the secretory pathway at different levels[121,122]. Finally, the three-dimensional structure of the ER could be also altered by disease proteins, as suggested, for example, for VAPB and huntingtin[123,124], which may contribute to the dysfunction of this organelle.

Alteration in the UPR machinery. There are only a few reports suggesting direct disturbance of proximal UPR components or the protein quality control machinery in neurodegeneration. In terms of genetic alterations, a polymorphism on the *XBP1* promoter was recently proposed as a risk factor for AD in the Chinese population[125]. This polymorphism was previously linked to the development of bipolar disorders and schizophrenia in Japan and was demonstrated to have a functional effect on *XBP1* transcription levels *in vitro*[126]. In the case of ALS, several mutations have been identified that are predicted to generate disturbances in ER proteostasis, including intronic variants of *PDI*[127], or mutations in genes involved in protein degradation such as *UBQLN2* (REF. 128) and *SQSTM1* (also known as *p62*)[129]. These few studies place ER-related disturbances as a possible genetic component of the aetiology of PMDs.

Direct interactions of disease-related proteins with UPR signalling components have been described (FIG. 3d). For example, mutant VAPB interacts with ATF6, inhibiting its transcriptional activity[130]. Similarly, a correlative study suggested that expression of mutant huntingtin triggers the selective inhibition of ATF6 but not other UPR branches[131]. Wild-type VAPB is located in the ER, where it enhances ER stress signalling through IRE1 and XBP1, whereas ALS-linked mutant VAPB has the opposite effect[132], enhancing the susceptibility of cells to ER stress[133]. Similarly, manipulation of the *LRRK2* (also known *PARK8*) homologue in *C. elegans*, the most frequent gene mutated in PD, leads to a high susceptibility to experimental ER stress, possibly owing to altered BiP expression, whereas expression of PD-linked mutant LRRK2 induces lethal ER stress[134,135]. Finally, early studies indicated that presenilin 1 might negatively influence IRE1 function, possibly owing to an abnormal proteolytical processing of this sensor[92,136]; however, the impact of presenilins on ER stress is still a topic of debate.

ER calcium homeostasis. The ER is the main intracellular calcium reservoir. Many ER chaperones and foldases require the direct binding of calcium to maintain optimal activity, which is perturbed by conditions that trigger ER calcium depletion. In fact, a classical ER stress agent used experimentally is thapsigargin, which inhibits the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) pump, leading to a passive release of ER calcium into the cytoplasm. There is a vast literature depicting abnormal release of calcium from the ER in several pathological conditions affecting the nervous system (reviewed in REF. 137).

Although there are many indirect ways of inducing sustained ER calcium release through signalling events, several examples suggest that a direct perturbation of ER calcium channels may occur in PMDs (FIG. 3e). An interactome analysis of mutant huntingtin revealed an abnormal association with the inositol trisphosphate

receptor (IP3R), which altered ER calcium homeostasis[138,139]. Similarly, inhibition of the ryanodine receptor (RYR) in a mouse model of HD provided significant neuroprotection[140]. In the context of PD, an interesting mechanism was recently proposed to affect ER calcium homeostasis. Stress induced by α-synuclein leads to the ERAD-mediated degradation of IP3R and RYR in dopaminergic neurons[141]. In agreement with this idea, altered expression of calcium channels was reported in PD-derived human tissue and animal models of the disease[141,142]. Conversely, a recent study was able to show the refolding of mutant lysosomal enzymes involved in Gaucher's disease by the artificial increment of ER calcium content, improving the activity of the calcium-dependent chaperone calnexin[143]. Finally, misfolded PrP sensitizes cells to ER stress, and this is associated with a drastic decrease in ER calcium concentration[52,144].

Regulation of disease genes by the UPR. Recent reports indicate that the expression of several well-described proteins involved in neurodegeneration may be directly regulated by proximal UPR components. Exploration of the *Xbp1* transcriptional network revealed that, in addition to controlling classical UPR target genes, XBP1s upregulates genes involved in the aetiology of AD, including components of the γ-secretase complex, cyclin-dependent kinase 5 (CDK5) and other factors[145]. Additional studies have shown that UPR signalling interferes with the early steps of APP maturation and processing[146,147]. It was also demonstrated that APP processing and amyloidogenesis are enhanced by PERK–eIF2α signalling via direct regulation of β-secretase 1 (BACE1)[148]. ATF4 can also regulate the expression of presenilins and can affect the activity of γ-secretases[149,150]. In the context of PD, ATF4 also regulates expression of the gene encoding parkin[151], whereas parkin controls Parkinson's disease 7 (*PARK7*; also known as *DJ-1*) transcription via a signalling pathway involving XBP1 (REF. 152). As ER stress is observed in most PMDs, these data suggest the occurrence of a vicious cycle in which ER stress may amplify disease progression not only by increasing protein aggregation but also by directly affecting genes involved in the aetiology of the disease.

In summary, all of the examples provided in this section depict distinct molecular mechanisms that may alter the function of the secretory pathway at different levels and converge to cause the irreversible alteration of ER proteostasis and neurodegeneration.

ER-hormesis and the vicious stress cycle

The ability of the UPR to maintain ER proteostasis could be exploited to develop therapeutic strategies to attenuate neurodegeneration. This idea has been reinforced through the use of the concept of 'hormesis', which involves the engagement of a preconditioning state via mild, non-lethal stress to induce adaptive reactions and protect the cell from a second, stronger injury[153,154]. In medicine, quick cycles of ischaemic preconditioning prepare the heart before surgery[155]. Research from the past few years has shown that mild ER stress also induces a hormetic response called ER-hormesis[156,157].

How is cellular protection in the ER-hormetic response achieved? One obvious interpretation, as proposed above, is that ER-hormesis promotes an increase in ER proteostasis capacities through the UPR and enables efficient folding and elimination of pathological misfolded proteins. By contrast, other studies have shown that ER-hormesis is not merely due to an upregulation of components of the folding machinery but also involves an antioxidant response and increased autophagy, which in turn improves oxidative folding, decreases cell death and reduces the load of protein aggregates[158–161]. ER-hormesis can be activated by all sorts of mutations or stimuli that result in mild protein misfolding in the ER. This is the case for mutations in the ER chaperone *ninaA* or alterations in the ERAD pathway in *D. melanogaster*, in which this condition protects photoreceptors against degeneration[63,162]. In *C. elegans*, hypoxic preconditioning induces the UPR, which promotes a protective response against further hypoxic injury[163]. In genetic and toxin-based models of PD, pretreatment with non-toxic doses of the ER stress-inducing agent tunicamycin (an inhibitor of *N*-glycosylation) protects against degeneration involving the selective activation of IRE1–XBP1 but not ATF4–CHOP pathways[161]. This protective effect was also associated with the upregulation of autophagy. Similarly, as discussed before, selective ablation of *Xbp1* in the nervous system reduces the pathology associated with mutant SOD1 or mutant huntingtin through upregulation of adaptive responses such as autophagy[47,164]. Thus, slight perturbations in the ER proteostasis network may provide neuroprotection through the engagement of adaptive ER-hormetic mechanisms.

Physiological impact of the UPR on the CNS?

The brain is the major subject of study in the context of ER stress compared with other tissues, as measured recently in the global publication records of different research areas[74]. Despite this, there is very little information available about basal levels of UPR activity in the nervous system, and this information is crucial to predict possible side effects of targeting the UPR using small molecules or gene therapy. In this section, we discuss the few studies that have suggested a physiological role for the UPR in different aspects of brain function.

The integrated stress response in learning and memory. Translational control through the phosphorylation of eIF2α and the expression of ATF4 have been shown to be involved in the process of memory consolidation[165]. Genetic and pharmacological evidence indicates that phosphorylation of eIF2α has inhibitory activity in long-term potentiation and memory consolidation[166] (FIG. 4a). Phosphorylation of eIF2α is part of the 'integrated stress response' in which several stress kinases that are not activated by ER stress converge in addition to PERK. These kinases include PKR, HRI (heme-regulated inhibitor kinase) and GCN2 (general control non-derepressible 2). Detailed studies are available indicating that PKR and GCN2 are responsible for translational control in synaptic plasticity and memory-related processes[167–169]. Remarkably, a recent study identified a

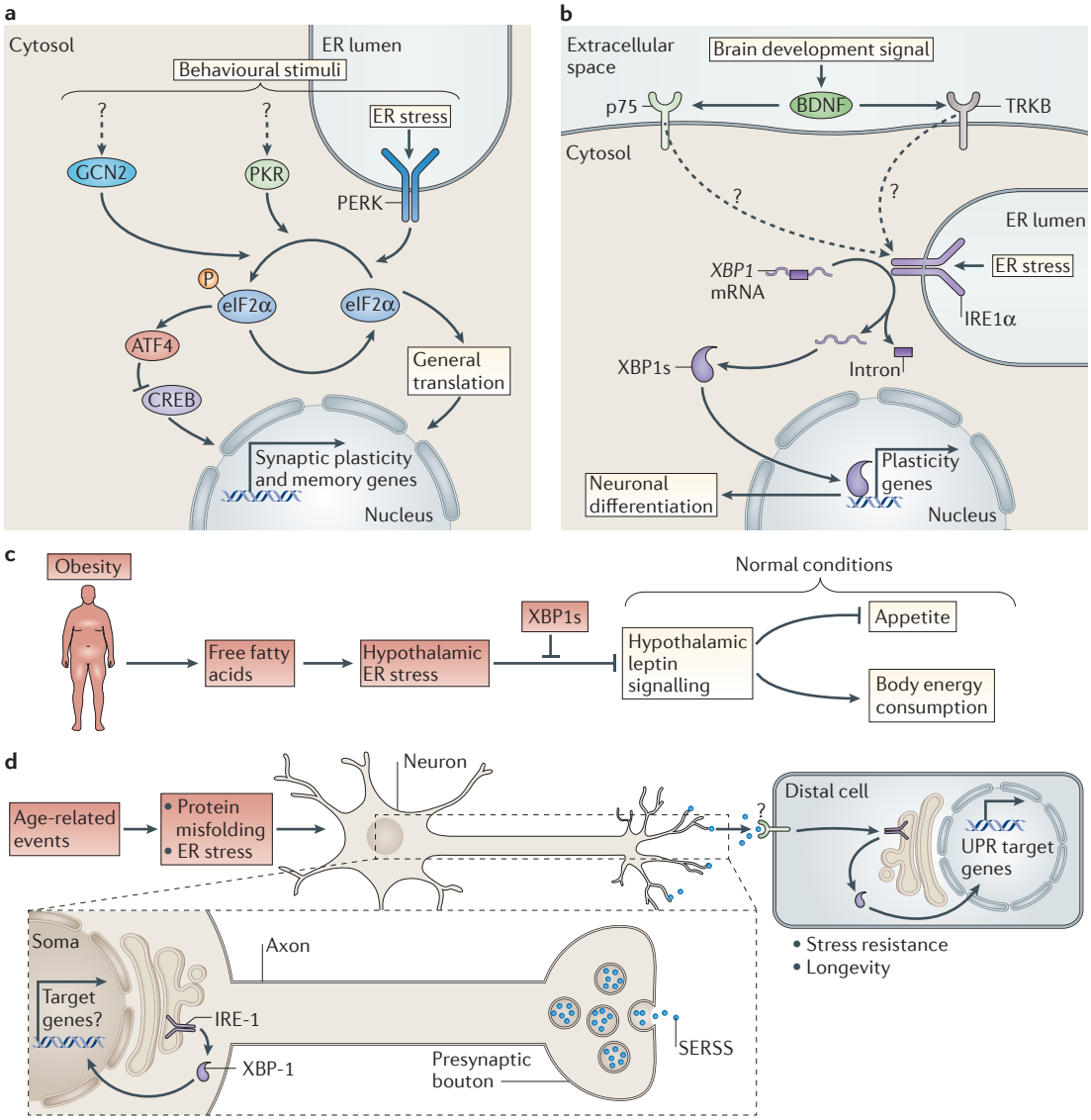

Figure 4 | **The role of the UPR in brain physiology.** Physiological activation of endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) are involved in several brain functions. **a** | Learning and memory involves eukaryotic translation initiation factor 2α (eIF2α) and activating transcription factor 4 (ATF4). eIF2α is phosphorylated by distinct kinases, including protein kinase RNA-like ER kinase (PERK) in an ER stress-dependent manner, or via RNA-activated protein kinase (PKR) or general control non-derepressible 2 (GCN2) in an ER stress-independent manner. Phosphorylation of eIF2α results in a generalized attenuation of translation and selective expression of ATF4, which promotes the inhibition of cyclic AMP-responsive element-binding protein (CREB) and, as a consequence, reduced expression of synaptic plasticity and memory genes. **b** | Brain development involves the UPR. During brain development, extracellularly secreted brain-derived neurotrophic factor (BDNF), acting via TRKB or p75 receptors, activates the inositol-requiring enzyme 1α (IRE1α)– X-box binding protein 1 (XBP1) signalling pathway, which promotes expression of plasticity and neuronal differentiation genes. **c** | The UPR interferes with hypothalamic functions and energy control. In obese patients, free fatty acids and other metabolites could induce ER stress in the hypothalamus, which in turn inactivates leptin-dependent control of appetite and energy consumption by the organism. These events might be inhibited by active, spliced XBP1 (XBP1s). Furthermore, these events may enhance the development of a metabolic syndrome. **d** | Mechanisms for cell-non-autonomous control of the UPR in the *Caenorhabditis elegans* nervous system. In *C. elegans*, activation of the UPR maintains protein homeostasis by cell-intrinsic and cell-non-autonomous mechanisms involving propagating stress signals from neurons to distal tissues. During ageing, there is a progressive loss of ER proteostasis, which causes an attenuation of stress responses. In the context of ageing, there is activation of *xbp-1* mRNA splicing and subsequent translation, and activation of target genes that trigger the synthesis of diffusible unknown signalling molecules termed secreted ER stress-inducing signals (SERSSs), which there is some evidence to suggest are transported as membrane-bound cargo to the axon terminal and released. SERSSs trigger a protective UPR response in distal intestinal cells by a process dependent on IRE-1 and XBP-1 expression. The precise mechanism is unknown but presumably involves SERSS binding to a receptor that signals to IRE-1. This trans-cellular signalling induces XBP-1 expression in the distal cell and increases stress resistance and longevity in *C. elegans*. Dashed arrows indicate that the mechanism is uncertain.

small molecule that inhibits the consequences of translational arrest under stress conditions. This compound significantly improved learning and memory of wild-type rats[170]. It is still an open question as to whether PERK is activated and contributes to memory acquisition. Besides, an interesting report indicated that targeting PERK expression in the mouse forebrain leads to alterations in performances on various behavioural tests[171]. In agreement with this, as mentioned previously, brain-specific deletion of *Perk* improved learning and memory and long-term potentiation in an AD mouse model[61]. However, at basal levels, no improvement in learning and memory parameters was reported in PERK-deficient animals. More direct studies are needed to define the functional impact of ER stress in neuronal signalling and cognition.

The development of the CNS and the UPR. *Xbp1* mRNA is upregulated in the brains of animals exposed to circumstances that also increase brain-derived neurotrophic factor (BDNF) expression, such as enriched environments[172] or exercise[173,174], and its splicing occurs in the hippocampus of animals subjected to behavioural stress[175]. XBP1 expression is also upregulated during brain development[176]. *In vitro* studies using primary neurons revealed that *Xbp1* mRNA splicing is triggered by BDNF to increase neurite outgrowth[176] (FIG. 4b). Gene expression profile analysis of primary neurons demonstrated that GABAergic markers, and not ER stress genes, are dependent on XBP1 expression upon BDNF treatment, including somatostatin, neuropeptide Y and calbindin[177]. Other studies indicated that the UPR regulates important developmental and physiological neuronal functions in *C. elegans* and *D. melanogaster*[178,179]. In *C. elegans*, the IRE-1–XBP-1 branch is needed for the trafficking of glutamate receptors to the plasma membrane[178]. Despite this evidence, analysis of XBP1 heterozygous animals' performance on a battery of behavioural tests did not reveal any dramatic phenotype[180]. In a recent study in flies, it was shown that RIDD specifically targets certain mRNAs (such as mRNA encoding Fatty acid transport protein[181]), a process required for photoreceptor differentiation in the developing retina[179]. These few studies suggest that IRE1–XBP1-dependent mechanisms may be of relevance in CNS development.

ER stress and hypothalamic function. The UPR has a well-established role in the control of energy metabolism in the liver and has a relevant impact on insulin resistance and diabetes[182]. An interesting study in the context of obesity revealed that XBP1 deficiency in the brain leads to leptin resistance[183]. In fact, exposure of XBP1-conditional-knockout mice to a high-fat diet led to a remarkable tendency to gain weight, and this weight gain correlated with changes in overall activity and energy consumption of the animals[183] (FIG. 4c). At the mechanistic level, the occurrence of ER stress and activation of the UPR was shown to inhibit leptin receptor signalling in the hypothalamus[184]. In the same brain region, XBP1-dependent gene expression correlated with the regulation of the circadian clock[185], and modulation of ER stress levels with salubrinal had a significant impact on sleep behaviour and hypothalamic activity[186]. These few studies illustrate the notion that UPR stress signalling in the brain may have broad effects on the whole physiology of the animal.

Ageing and cell-non-autonomous control of the UPR. Very recent studies in *C. elegans* have uncovered an interesting and revolutionary concept that the UPR may have cell-non-autonomous effects in different (non-neuronal) organs that are controlled by signals derived from subsets of neurons[187]. This idea has been proposed before in the same organism by Morimoto's group[188] in the induction of the heat shock response. Cell-non-autonomous UPR induction was first shown to determine the susceptibility to pathogens by modulating innate immunity in the periphery through neuronal control[189] (FIG. 4).

A recent study in *C. elegans* indicates that XBP-1 expression has an important role in prolonging lifespan through a cell-non-autonomous mechanism[190]. XBP-1 expression has been linked to longevity, possibly by crosstalk with classical pathways involved in the process, including insulin–insulin growth factor-1 signalling and FOXO transcription factors[191]. Interestingly, during ageing in this organism, the capacity to induce the UPR and other stress responses is attenuated, suggesting a general dysfunction of the cell, so that it is unable to adjust to alterations in the proteome and to manage proteotoxic stress[188,190]. Remarkably, the ectopic expression of XBP-1 in neurons initiates a UPR reaction in non-neuronal tissue, extending the lifespan of the worm (FIG. 4d). The activation and propagation of cell-non-autonomous UPR signals in this context involves neuronal activity and the release of neurotransmitters[190]. Furthermore, a recent report also indicated that 'trans-cellular communication' of stress signalling in worms may occur between the nervous system and peripheral tissue in the handling of protein folding stress[192]. Trans-cellular stress signalling was shown to maintain whole-organism proteostasis through the modulation of the expression of chaperones such as HSP90 and transcription factors of the FOXO family[192]. It remains to be determined whether cell-non-autonomous control of the UPR operates in mammals.

These recent reports are the initial steps towards defining the physiological relevance of the UPR within the nervous system and have so far depicted a scenario in which the pathway may have a broad homeostatic role in controlling not only cognitive processes but also energy metabolism throughout the body, innate immunity and ageing-related processes. The concept of 'awareness responses' is emerging in which the propagation of stress signals through the nervous system and other organs may trigger a preconditioning and/or adaptive stage in the whole organism to maintain global proteostasis.

Concluding remarks

The spectrum of biological processes in which ER stress has relevant activities is increasing each year. Genetic manipulation of proximal UPR components has demonstrated novel physiological functions of the pathway in energy and lipid metabolism, cell differentiation,

innate immunity and other processes[193,194]. ER stress has been extensively studied in various diseases that affect the nervous system, and most attention has been placed on PMDs. Functional studies manipulating ER stress responses in models of neurodegeneration highlight the idea that distinct UPR signalling modules control specific cellular events that can specifically affect brain diseases through non-overlapping mechanisms.

It is becoming clear that, depending on the intensity and duration of the stress stimuli, and the nature of the perturbation to the secretory pathway, targeting the UPR may lead to neuroprotection or, conversely, to an exacerbation of the disease condition, whereas in certain pathologies no effects at all may be observed despite evident ER stress induction (TABLE 2). Addressing this issue is essential to be able to predict the possible side effects of future therapeutic interventions that target the UPR in the context of brain diseases. In addition, applications in the area of biomarkers may be available in the near future through the identification of specific patterns of stress-gene expression that may reflect the disease state of the brain. It is also important to highlight the fact that only a few studies have directly addressed the impact of PERK on neurodegeneration, because most of the manipulations have been performed at the level of eIF2α phosphorylation or its downstream responses, which are not exclusive to the ER stress–UPR pathway.

The most recognized function of the UPR in physiology is the support of secretory cell function; however, this concept has not been directly addressed in the nervous system. As discussed above, in multiple sclerosis and axonal injury models, Schwann cells and oligodendrocytes are the major cell types affected in the pathology and are the cells that are most vulnerable to ER stress manipulations. It remains to be determined whether myelin synthesis per se constitutes a physiological source of ER stress. With this in mind, it is an open question as to whether the UPR can modulate the differentiation of these cell types, as observed in specialized secretory cells[7]. Neuropeptide-producing neurons are also an attractive population of brain cells that need to be investigated in detail in the context of the UPR. Another area of research that is fully open is brain inflammation. The UPR has a demonstrated impact on various immune cells, in which it regulates the secretion of pro-inflammatory cytokines and innate immunity signals[195]. Because most pathologies of the CNS involve brain inflammation, the actual impact of the UPR on microglial and astrocyte function should be studied in depth. The advances in the field in the past 5 years are revolutionary, owing to the generation of mice in which essential UPR components have been genetically modified and to the recent discovery of small molecules that target essential UPR components[196]. Additional comparative and systematic studies are needed to better define the real therapeutic value of manipulating ER stress levels and also to outline possible side effects, with a special emphasis on monitoring the consequences in cognitive aspects of the nervous system.

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The authors declare no competing interests.