Endoplasmic reticulum proteostasis impairment in aging

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Summary
Perturbed neuronal proteostasis is a salient feature shared by both aging and protein misfolding disorders. The proteostasis network controls the health of the proteome by integrating pathways involved in protein synthesis, folding, trafficking, secretion, and their degradation. A reduction in the buffering capacity of the proteostasis network during aging may increase the risk to undergo neurodegeneration by enhancing the accumulation of misfolded proteins. As almost one-third of the proteome is synthesized at the endoplasmic reticulum (ER), maintenance of its proper function is fundamental to sustain neuronal function. In fact, ER stress is a common feature of most neurodegenerative diseases. The unfolded protein response (UPR) operates as central player to maintain ER homeostasis or the induction of cell death of chronically damaged cells. Here, we discuss recent evidence placing ER stress as a driver of brain aging, and the emerging impact of neuronal UPR in controlling global proteostasis at the whole organismal level. Finally, we discuss possible therapeutic interventions to improve proteostasis and prevent pathological brain aging.

Key words: aging; endoplasmic reticulum; endoplasmic reticulum stress; protein misfolding disorders; unfolded protein response.

Introduction
As the world population gets older, dementia emerges as a major public health issue worldwide, particularly in middle- and middle-to-high-income countries. The prevalence of dementia increases exponentially with age, affecting 5–10% of people over 65, and about 50% of people over 85. In 2011, dementia was estimated to affect 35.6 million people around the world, and it is expected to reach about 135 million by 2050 (Brayne, 2007; World Health Organization and Alzheimer’s Disease International 2012). Reduced cognitive function is a common trait present in elderly individuals, which correlates with substantial alterations to functional synapses and normal neuronal physiology at the cellular and molecular level (Leal & Yassa, 2015). Accordingly, a significant percentage of aged individuals will manifest some sort of dementia in the form of a collection of neurodegenerative diseases, transposing the line between normal aging (healthspan) to pathological brain aging (Brayne, 2007). Recently, several interconnected processes have been defined as the hallmarks of aging, where substantial alterations to cellular proteostasis is proposed as one of the major pillars of aging (Lopez-Otin et al., 2013; Kennedy et al., 2014).

The proteostasis network is decomposed into different subpathways highly conserved across evolution and comprehends a collection of mechanisms related to protein synthesis, folding, trafficking, secretion, and degradation distributed in different compartments inside the cell (Balch et al., 2008; Powers & Balch, 2013). The main players of this network include chaperones and foldases, the ubiquitin–proteasome system, the autophagy pathway, the heat-shock response, the unfolded protein response (UPR), the integrated stress response, the endoplasmic reticulum (ER)-associated degradation machinery (ERAD), the mitochondrial UPR, and the mechanisms controlling redox balance (Balch et al., 2008). Those processes are dynamic and tightly coordinated by quality control systems to avoid proteotoxicity and ensure that unfolded or misfolded proteins do not accumulate into cytotoxic aggregates (Labbadia & Morimoto, 2014). Various pathological conditions affecting the nervous system share common molecular features despite presenting different clinical manifestations, highlighting the presence of abnormal protein aggregates in the brain of affected individuals (Walker et al., 2015). These age-related diseases are classified as protein misfolding disorders (PMDs) and include Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), Huntington’s disease (HD), prion-related disorders (PrDs), among others (Soto, 2003). Importantly, one of the main nodes of the proteostasis network involved in aging and PMDs is the UPR and the occurrence of abnormal levels of ER stress. Recent advances in model organisms have uncovered the significance of the UPR to the control of global proteostasis during aging, where the nervous system has a central role in monitoring alterations in the health of the proteome to adjust the capacity of the cell to cope with ER stress in various peripheral tissues. Here, we discuss new concepts illustrating the functional relevance of the UPR to organismal aging across species and its significance as a risk factor to develop neurodegenerative diseases.

The unfolded protein response
The ER is the main site for the synthesis and folding of around one-third of the total proteome of a cell (Braakman & Bulleid, 2011). Considered a key component of the proteostasis network, ER-located proteins regulate folding and quality control through the activity of multiple chaperones, foldases, and co-factors that assist the folding of nascent proteins as well as degradation pathways, thus preventing abnormal protein aggregation and resultant proteotoxicity (Eiglaard & Helenius, 2003; Kourtis & Tavernarakis, 2011; Hetz et al., 2015). Stressful stimuli such as hypoxia (Badiola et al., 2011), nutrient deprivation (Szegoedi et al., 2006), increased protein oxidation (Santos et al., 2009), and
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disturbance of the secretory pathway (Badr et al., 2007) may lead to an excessive accumulation of misfolded proteins at the ER, a process termed ER stress (Walter & Ron, 2011; Hetz, 2012). To cope with ER stress, a highly conserved signaling pathway is engaged known as the UPR (Wang & Kaufman, 2016). The UPR is initiated by the activation of at least three types of stress sensors including inositol-requiring enzyme-1 (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6). IRE1 catalyzes the unconventional splicing of the mRNA encoding X-box binding protein-1 (XBP1) (Yoshida et al., 2001; Calfon et al., 2002; Lee et al., 2002), resulting in the expression of an active transcription factor called XBP1s that controls the expression of a cluster of genes related to folding and quality control mechanisms (Hetz et al., 2011). Additionally, IRE1 also degrades several mRNAs, ribosomal RNAs, and microRNAs through a process known as regulated IRE1-dependent decay (RIDD), having an impact on different processes including inflammation and apoptosis (Maurel et al., 2014). IRE1 also engages distinct stress pathways, including JNK and NF-xB, through the binding of adapter proteins (Hetz et al., 2015). Activation of PERK leads to the phosphorylation of the eukaryotic translation initiation factor 2 alpha (eIF2α), which in turn inhibits translation decreasing protein influx into the ER (Ron & Walter, 2007). PARadoxically, some mRNAs, including activating transcription factor 4 (ATF4), are differentially translated, leading to the upregulation of genes related to redox homeostasis, amino acid metabolism, autophagy, and apoptosis control (Harding et al., 2003; Ye & Koumenis, 2009; B’Chir et al., 2014). Moreover, PERK activation has been shown to modulate the activity of nuclear factor erythroid 2-related factor 2 (NRF2) and forkhead box O (FOXO), linking this pathway to the antioxidant response, insulin responsiveness, and autophagy (Chevet et al., 2015). Under ER stress conditions, ATF6 translocates to the Golgi apparatus where it is cleaved releasing ATF6f, a cytosolic active form. ATF6f exerts its action at the nuclear level as a transcription factor regulating genes associated with ERAD, in addition to enhancing XBP1 mRNA transcription (Yamamoto et al., 2007). Importantly, the control of gene expression by the UPR depends on the cellular context and the stimuli considering that UPR transcription factors can interact with other proteins to drive specific responses, in addition to be regulated by several post-translational modifications (Hetz et al., 2015). Under chronic ER stress, the UPR triggers apoptosis through different mechanisms that involve the upregulation of CHOP, the induction of oxidative stress, exacerbated RIDD, upregulation of pro-apoptotic components of the BCL-2 family, among other mechanisms (Tabas & Ron, 2011; Urra et al., 2013). Thus, under conditions of ER stress, the UPR reprograms the cell toward adaptation, sustaining cell function or the engagement of cell death programs to eliminate irreversibly damaged cells.

ER proteostasis and aging in simple model organisms

During aging, organisms gradually accumulate intracellular aggregates composed by misfolded proteins, an event that is associated with a prominent decline in the buffering capacity of the proteostasis network and a consequent decrease in tissue and cellular function (Fig. 1) (Taylor & Dillin, 2011; Triplett et al., 2015). Several studies in model organisms have uncovered the significance of UPR signaling to the aging process, associated with protection against proteotoxicity (Ben-Zvi et al., 2009; Labunsky et al., 2014). For example, caloric restriction has been used as a major strategy to prevent the adverse effects of aging on healthspan (Riera & Dillin, 2015). In yeast, this intervention correlates with increased expression of HAC1, the functional homologue of XBPIs (Choi et al., 2013). Remarkably, genetic ablation of HAC1 abolges the lifespan extension conferred by caloric restriction (Choi et al., 2013). Other studies indicated that the deletion of distinct UPR-target genes impact replicative lifespan in yeast, a process dependent on the Ire1p/HAC1 axis (Labunsky et al., 2014). Furthermore, genetic modifications to improve the activity of the UPR enhance replicative lifespan in Saccharomyces cerevisiae (Cui et al., 2015).

Studies in Caenorhabditis elegans have revealed a fundamental role of the UPR in adjusting organismal proteostasis during aging through a neuronal control. Exposure of Caenorhabditis elegans to pharmacological inducers of ER stress indicated that the ability of aged worms to respond is significantly reduced compared with young animals (Ben-Zvi et al., 2009). Interestingly, the same observation was reported when animals were stimulated with heat shock (Ben-Zvi et al., 2009), suggesting global proteotoxic defects during aging. Enforced expression of heat-shock factor 1 (HSF-1) or the FOXO-transcription factor DAF-16 restores proteostasis of aged worms (Ben-Zvi et al., 2009). Loss-offunction studies in Caenorhabditis elegans demonstrated that lifespan extension conferred by XBPI expression is dependent on insulin/IGF-1/FOXO signaling, a classical pathway associated with aging (Henis-Korenblit et al., 2010; Douglas et al., 2015). Importantly, lifespan extension was only achieved through the parallel interaction between XBPI and FOXO-transcription factor DAF-16, which acts in conjunction to genes related to longevity (Henis-Korenblit et al., 2010). According to these observations, Taylor and Dillin demonstrated that the selective overexpression of XBPIs in neurons or intestine strongly reverts the age-related susceptibility to ER stress stimulation (Table 1) (Taylor & Dillin, 2013). Remarkably, the overexpression of XBPIs in neurons has a strong impact on lifespan extension, augmenting animal survival up to 30%. A recent study also indicated that loss-of-function mutations in distinct subunits of translation initiation factor elf-3 confer a 40% extension in the lifespan of Caenorhabditis elegans through a DAF-16-dependent and UPR-independent pathway (Cattie et al., 2016), suggesting that different nodes of the proteostasis network significantly contribute to aging in worms.

Studies in flies have also defined contributed to define the relevance of the UPR to the aging process. Intestinal stem cells in Drosophila melanogaster promote a regenerative response upon UPR activation, a process deregulated during aging (Wang et al., 2014). Later, Wang et al. demonstrated that PERK is specifically activated in intestinal stem cells, having a functional role in promoting healthspan in flies. However, chronic engagement of this pathway becomes deleterious during aging in Drosophila melanogaster (Wang et al., 2015). A previous study also indicated that Xbp1 is both sufficient and required to limit intestinal stem cell proliferation (Wang et al., 2014). Recently, the same group reported that engagement of the Ire1/Xbp1 branch also results in lifespan extension in the same model under dietary restriction. The activation of Ire1/Xbp1 pathway in enterocytes under dietary restriction has a positive impact on lifespan of gut cells by regulating lipid synthesis (Luis et al., 2016). Overall, the functional significance of ER stress signaling to lifespan control has been inferred from several studies in simple model organisms.

Cell-nonautonomous control of organismal aging by the UPR

A novel concept is emerging based on research using fly and worm models of aging, indicating that the ER proteostasis network promotes health and lifespan through cell-nonautonomous mechanisms, impacting whole organismal proteostasis (Mardones et al., 2015). Studies in Caenorhabditis elegans revealed that besides its importance in individual
cells, the UPR acts as a key player in modulating global organism adaptability to stress during aging by integrating information at the level of the nervous system (Martinez et al., 2016a). Accordingly, UPR can be activated on a cell-nonautonomous manner (Taylor & Dillin, 2013). The ectopic expression of XBP1s in neurons is able to engage a distal UPR activation in the intestine, thus increasing stress resistance and longevity in Caenorhabditis elegans (Taylor & Dillin, 2013). These results suggest that the nervous system may act as a central integrator and adjustor of global proteostasis, with possible major distal effects in the intestine. Importantly, other studies previously demonstrated that neuronal UPR regulates the innate immunity in the gut on a cell-nonautonomous manner (Martinez & Hetz, 2012; Sun et al., 2012; Aballay, 2013). Chromatin remodeling factors in neurons can also engage ER stress responses through a cell-nonautonomous mechanism (Kozlowski et al., 2014). Thus, accumulating evidence supports the idea that when an organism is exposed to environmental or pathogenic challenges, the ability of the nervous system to integrate these signals through the activation of the UPR favors the maintenance of homeostasis in various peripheral organs (Mardones et al., 2015). A similar model has been proposed for the heat-shock response by Morimoto's group, where HSF-1 in neurons regulates global responses to aging in the gut (Morley & Morimoto, 2004; van Oosten-Hawle & Morimoto, 2014a; Douglas et al., 2015). Importantly, cell-nonautonomous control of aging-related pathways has been extensively described in different model organisms mediated by distinct signaling molecular mediators (Taylor et al., 2014; Leiser et al., 2015; Schinzel & Dillin, 2015). A recent study indicated that PERK is activated in intestinal stem cells by JAK/Stat signaling in response to ER stress in neighboring cells, regulating intestinal homeostasis and lifespan in flies (Wang et al., 2015). A cell-nonautonomous mechanism has been also described in mammals, where overexpression of XBP1s in the hypothalamus modulates global energy balance through the propagation of signals to the liver and adipose tissue to adjust energy metabolism (Williams et al., 2014). Furthermore, the concept of 'transcellular chaperone signaling' was proposed in Caenorhabditis.
er stress and increased susceptibility to ER stress-dependent apoptosis (Song et al., 2008). Another study demonstrated similar observations in the pancreas of mice (Naidoo et al., 2014). Additionally, aged macrophages exhibit diminished IRE1 activation and increased susceptibility to ER stress-dependent apoptosis (Song et al., 2013). These findings suggest that the ability to engage the UPR may be disrupted during aging; however, the functional significance of these observations is unknown (Fig. 2).

In contrast, several reports suggest that chronic ER stress is associated with aging in multiple tissues. Increased levels of CHOP, ATF4, and XBP1s were observed in primary osteocytes from aged mice when compared to adult mice exposed to ER stress-inducing agents (Chailil et al., 2015). Similar results were reported in stromal cells from adipose tissue of aged mice, associated with augmented levels of BIP, CHOP, ATF6, and phosphorylated IRE1 (Ghosh et al., 2015). CHOP was also shown to be induced at baseline in muscular tissue of the hindlimb of aged rats (Baehr et al., 2016). Of interest, gene expression profile studies demonstrated that UPR-target genes are one of the most affected pathways in bone marrow during aging (Kannan et al., 2016). At the level of the central nervous system, phosphorylation of CHOP, ATF6, GADD34, ATF4, and eIF2α are also upregulated in the retina of aged rats (Lenox et al., 2015).

ER stress signaling components have been shown to interact with classical aging-related pathways suggesting a functional interconnection. For example, in the context of HD, we showed that XBP1 negatively regulates FOXO1 levels (Vidal et al., 2012). Several reports have also linked ER stress responses with the control of autophagy (reviewed in Vidal et al., 2014), a central pathway involved in proteostasis control (Kaushik & Cuervo, 2015). Insulin signaling is also linked to IRE1 function, as demonstrated in models of diabetes and obesity (Ozcan et al., 2004). Overall, these studies depict a general concept where mammalian aging is directly associated with the occurrence of chronic ER stress. Those findings may be explained by accumulative ER damage rather than an attenuation of UPR responses. Currently, functional analysis is needed to define the actual contribution of ER proteostasis to mammalian aging. Since a variety of mouse models are available to target specific UPR components in various tissues (Cornejo et al., 2013), the means to answer this fundamental question are already available.

**Aging as a risk factor to undergo neurodegeneration: a role of ER stress?**

Abnormal aggregation of specific proteins is a hallmark of age-related neurodegenerative diseases. Increasing evidence indicates that despite the fact that PMD-related proteins distribute in different subcellular locations and have distinct binding partners, a common pathological consequence of their accumulation is the occurrence of ER stress. This mechanistic convergence is explained by the observation that disease-related proteins actually disrupt the function of one or more components of the proteostasis network, highlighting the inhibition of ERAD, altered vesicle trafficking between the ER and Golgi, perturbed ER calcium homeostasis, autophagy dysregulation, and abnormal interactions with ER chaperones (Hetz & Mollereau, 2014; Vidal et al., 2014; Kaushik & Cuervo, 2015).

Importantly, with the exception of HD, familiar cases of PMDs account for less than 10% of cases, indicating that protein aggregation occurs in the absence of genetic mutations to the affected proteins. This observation suggests that alteration in different components of the proteostasis network during aging may contribute to protein aggregation. The involvement of ER stress in PMDs is highly complex, acting both as protective or detrimental (Hetz & Mollereau, 2014; Scheper & Hoozemans, 2015; Freeman & Mallucci, 2016). Indeed, the activity of the UPR in neurodegenerative diseases could either enhance or reduce neurodegeneration, depending on the process that is modulated by specific ER stress signals and the particular disease studied. A strong correlation between ER stress markers and signs of neurodegeneration has been reported in human postmortem tissue and animal models of PMDs. Remarkably, human neurons derived from induced pluripotent stem cells of AD, PD, and ALS patients revealed that ER stress is a prominent feature of this disease model (Chung et al., 2013; Kondo et al., 2013; Matus et al., 2014; Lee & Huang, 2017). Other studies also suggest that ATF4 may enhance axonal degeneration in AD through cell-autonomous mechanisms (Baleriola et al., 2014; Wei et al., 2015).

Importantly, the repressive effects of ER stress over protein synthesis were shown to contribute to the cognitive impairment observed in AD and PD models by blocking the expression of synaptic proteins (Moreno et al., 2012, 2013; Freeman & Mallucci, 2016). Studies in...
Drosophila melanogaster (Loewen & Feany, 2010; Casas-Tinto et al., 2011) and Caenorhabditis elegans (Safra et al., 2013) reported a functional role of XBP1 in neurodegeneration in AD. Interestingly, a polymorphism in the XBP1 promoter previously associated with bipolar disorders and schizophrenia (Kakiuchi et al., 2003; Du et al., 2008; Kim et al., 2009) was also pointed as a risk factor to develop AD in the Chinese population (Liu et al., 2013). In agreement with these findings, a new physiological function of XBP1 was proposed in the hippocampus in the control of learning and memory processes (Martinez et al., 2016b).

Genetic ablation of XBP1 in the nervous system uncovered a dynamic interconnection between the UPR and the autophagy pathway to handle protein aggregation. XBP1 deficiency protects against the development of experimental HD and ALS due to an increase in autophagy levels (Hetz et al., 2009; Vidal et al., 2012). In the context of PD, XBP1 deficiency also provided neuroprotection associated with the basal upregulation of several components of the ER proteostasis network, possibly reflecting the induction of nonlethal stress levels at the substantia nigra (Valdes et al., 2014). The concept of hormesis was proposed as an adaptive mechanism where a mild perturbation to neuronal proteostasis triggers compensatory mechanisms that enhance the capacity of the cell to cope with stress (Mollereau et al., 2016). In fact, treatment of animals with nonlethal doses of the ER stress agent tunicamycin (an inhibitor of N-glycosylation) provides protection against PD possibly due to the induction of autophagy (Fouillet et al., 2012). Many other functional studies illustrate the therapeutic consequences of enforcing UPR adaptive outputs in ALS, PD, and HD (reviewed in Hetz & Mollereau, 2014; Freeman & Mallucci, 2016; Scheper & Hoozemans, 2015).

Recent evidence suggests that ER stress may underlay the differential neuronal vulnerability observed in neurodegenerative diseases, where most of the advances have been reported in ALS models (Rozas et al., 2016; Ruegsegger & Saxena, 2016). Disruption to the ER folding network is emerging as a key factor underlying the susceptibility of specific neuronal populations to undergo neurodegeneration (Filezac de L’Etang et al., 2015). In addition, genetic evidence has placed the ER proteostasis network in the etiology of ALS as mutations in two-disulfide isomerase (PDIA1 and ERp57) were proposed as risk factors to develop ALS (Gonzalez-Perez et al., 2015; Woehlbier et al., 2016). Alterations to the ER folding network may result in abnormal synthesis of synaptic proteins, having a negative effect on the integrity of neuromuscular junctions and neuronal connectivity (Bernard-Marissal et al., 2012, 2015; Woehlbier et al., 2016). Similarly, genetic inactivation in BiP or its cofactor SIL1 results in spontaneous degeneration, leading to abnormal protein aggregation during aging (Zhao et al., 2005; Jin

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**Fig. 2** Endoplasmic reticulum (ER) stress in aging across species. The aging process is directly associated with a range of specific alterations in distinct components of the ER proteostasis network in different tissues, highlighting changes in components of the unfolded protein response and the folding machinery.
The UPR participates in the adjustment of energy and lipid metabolism, the importance of the UPR to brain inflammation and the activity of Glimcher, 2015). In this context, future efforts should address the perturbations to ER function possibly because their metabolic state depends on the basal activity of the UPR. Furthermore, the UPR may operate as a mechanism to handle abnormal protein aggregation, increasing the risk to develop neurodegenerative diseases.

Concluding remarks

Imbalance of neuronal proteostasis is one of the pathological hallmarks of aging, and understanding its molecular defects will contribute to develop strategies to intervene age-associated disorders. Because the nervous system is highly dynamic and plastic, the manifestation of clinical features in patients arises very late, after severe damage has already occurred. Likely, it is predicted that the development of strategies to improve the quality of the aging process will substantially reduce the probability to undergo PMDs. Despite the fact that proteostasis is composed of a complex network of individual interconnected signaling pathways, recent findings suggest that the maintenance of ER physiology is a prominent molecular target to prevent age-related diseases affecting the nervous system. The involvement of ER stress in the biology of aging is complex as illustrated by most recent advances. The activity of the ER proteostasis network may not only operate as a mechanism to handle abnormal protein aggregation, but it is also proposed as an adjuster of brain function through fine-tuning synaptic function. Specific neuronal populations are highly vulnerable to perturbations to ER function possibly because their metabolic state depends on the basal activity of the UPR. Furthermore, the UPR may orchestrate repair processes of the nervous system by controlling the expression of neurotrophins such as BDNF, and the regenerative capacity of axons and stem cells pools (Castillo et al., 2015; Martinez et al., 2016b; Onate et al., 2016). Regarding inflammatory reactions, the UPR is known to have important functions in macrophages and dendritic cells by modulating the secretion of pro-inflammatory cytokines (Bettigole & Gilmcher, 2015). In this context, future efforts should address the importance of the UPR to brain inflammation and the activity of astrocytes, microglia, and oligodendrocytes during aging. The fact that the UPR participates in the adjustment of energy and lipid metabolism, an additional layer of complexity, could be also explored to link the UPR with brain aging. Finally, the discovery of cell-nonautonomous UPR responses and its relation to healthspan control adds a new concept as ER stress-related signals in the brain may influence the capacity of the whole organism to adapt and cope with ER stress. All those aspects should be considered in future studies aiming to define the relative impact of ER stress on mammalian brain aging and its significance as a risk factor to develop neurodegenerative diseases.

Several novel small molecules are available to target selective UPR components and reduce ER stress levels (Table 2; Hetz et al., 2013; Malý & Papa, 2014; Gallagher & Walter, 2016; Gallagher et al., 2016; Axten, 2017), which promises possible new avenues to intervene the aging process. Importantly, some of these compounds have already been tested in preclinical models of PMDs (Table 2). However, it is important to consider possible side effects as the activity of the UPR has been linked to the physiology of many peripheral organs and the long-term administration of UPR-targeting drugs is predicted to induce liver failure, altered immune system function, pancreatic problems, among others maladies (Dufey et al., 2014). In this scenario, gene therapy is emerging as a strategy to locally reduce ER stress by delivering adaptive components of the UPR (i.e., XBP1s, BiP) specifically into the brain regions affected by distinct neurodegenerative diseases (Valenzuela et al., 2016). Overall, although the UPR is emerging as a central and evolutionarily conserved modulator of the normal process of aging, data available in mammalian systems are still correlative and remain to be functionally explored. As the UPR field has greatly evolved in the last five years in terms of generation of animal models and pharmacological tools, it is expected to witness future advances to underscore the significance of the UPR to brain aging and its relation to neurodegenerative diseases.

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Table 2 Pharmacological modulation of the unfolded protein response (UPR). A summary is presented of chemically synthesized compounds to activate or inhibit the different UPR signaling components, including their efficacy in preclinical models of neurodegenerative diseases. Those components may emerge as candidates for lifespan/healthspan extension in the future (Malý & Papa, 2014; Gallagher et al., 2016; Gallagher & Walter, 2016; Plate et al., 2016; Axten, 2017).

| UPR branch related | Drug | Molecular target | Effect | Readout | Model/disease |
|--------------------|------|------------------|--------|---------|---------------|
| PERK               | GSK2656157 and GSK2606414  | PERK kinase domain | Inhibitor | Inhibition of eIF2α phosphorylation | Mouse/PrD, Tauopathies |
|                    | Integrate stress response  | Guanine nucleotide | Inhibitor | Decreased ATF4 expression | Mouse/PrD — memory and cognition |
|                    | inhibitor (ISRIB)          | exchange factor eIF2B |        |         |               |
|                    | Salubrinal                 | Binding GADD34 | Inhibitor | Repression of translation, decrease in protein misfolding overload | Rat-mouse/ALS, PD, Prion disease, spinal cord injury, multiple sclerosis, Charcot-Marie-Tooth 1B |
|                    |                 | phosphatase complex |        |         | Mouse/ALS, Charcot-Marie-Tooth 1B |
|                    | Guanabenz and Sephin1 | PPP1R15A eIF2α phosphatase | Inhibitor | Repression of translation, decrease in protein misfolding overload | Mouse/cancer models |
|                    |                 | Kinase inhibiting RNase inhibitors 3 and 6 (Kira 3 and Kira 6) | Inhibitor | Decrease of mRNA XBP1 splicing | Mouse/diabetes and retinal damage |
| IRE1α              | MKC-3946 SFT-083010 | Kinase inhibiting RNase | Inhibitor | Reduce IRE1α signaling | |
|                    |                | attenuators 3 and 6 (Kira 3 and Kira 6) | Kinase domain |        |               |
| ATF6               | Ceapin-A1             | Activator | Induction of UPR-regulated genes profile expression | Cells |
|                    | Ceapin-A7             | Activator | Induction of UPR-regulated genes profile expression | Cells |

et al., 2014). Taken together, these studies suggest that alterations to the function of the ER during aging may contribute to synaptic dysfunction and abnormal protein aggregation, increasing the risk to develop neurodegenerative diseases.
Conflict of interest

Authors declare that they have no conflict of interest.

References

Abaylal A (2013) Role of the nervous system in the control of proteostasis during innate immune activation: insights from C. elegans. PLoS Pathog. 9, e1003433.

Axtens JM (2017) Protein kinase R/PKR-like endoplasmic reticulum kinase (PERK) inhibitors: a patient review (2010–2015). Expert Opin. Ther. Pat. 27, 37–48.

Badiola N, Penas C, Minano-Molina A, Barneda-Zahonero B, Fado R, Sanchez-Opazo G, Comella JX, Sabria J, Zhu C, Blomgren K, Casas C, Rodriguez-Alvarez J (2011) Induction of ER stress in response to oxygen-glucose deprivation of cortical cultures involves the activation of the PERK and IRE-1 pathways and of caspase-12. Cell Death Dis. 2, e149.

Badr CE, Hewett JW, Breakefield XO, Tannous BA (2007) A highly sensitive assay for measuring the activities of human caspases-8, -9 and -3. J. Neurosci. Res. 85, 1385–1391.

Baehr LM, West DW, Marcotte G, Marshall AG, De Sousa LG, Baar K, Bodine SC (2014) Baleriola J, Walker CA, Jean YY, Crary JF, Troy CM, Nagy PL, Hengst U (2014) Correction: Functional processing the XBP-1 mRNA. Cell Death Dis. 5, e149.

Chevet E, Hecz T, Samali A (2015) Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis. Cancer Discov. 5, 586–597.

Choi KM, Kwon YY, Lee CK (2013) Characterization of global gene expression during assurance of lifespan extension by caloric restriction in budding yeast. Exp. Gerontol. 48, 1455–1468.

Chung CY, Khurana V, Auluck PK, Tardif DF, Mazzulli JR, Soldner F, Baru V, Lou Y, Freyzon Y, Cho S, Mungenast AE, Muffat I, Mitopilava M, Puth M, Ji NT, Schule B, Lippard SJ, Tsai LH, Krainc D, Buchwald SL, Jaenisch R, Lindquist S (2013) Identification and rescue of alpha-synuclein toxicity in Parkinson patient-derived neurons. Science 342, 983–987.

Cornevo VH, Pihan V, Pidal RL, Hecz T (2015) Role of the unfolded protein response in organ physiology: lessons from mouse models. IUBMB Life 65, 962–975.

Cui HI, Liu XG, McCormick M, Wasko BM, Zhao W, He X, Yuan Y, Fang BX, Sun XR, Kennedy BK, Suh Y, Zhou ZJ, Kaeberlein M, Feng WL (2015) PmT1 deficiency enhances basal UPR activity and extends replicative lifespan of Saccharomyces cerevisiae. Age (Dordr) 37, 9788.

Douglas PM, Baird NA, Simic MS, Uhlein S, McCormick MA, Wolff SC, Kennedy BK, Dillon A (2015) Heterotypic signals from nervous system-derived neurons in later life, G. Martínez et al. Published by the Anatomical Society and John Wiley & Sons Ltd.

Hetz C (2012) The unfolded protein response: controlling cell fate decisions under stress. Nat. Rev. Neurosci. 15, 107–118.

Hofmaier IUBMB Life 342, 92–96.

H GST 16, 158–170.

Ioffe A, Levit C, Virgin A, Robin M, Dourlen P, Rieusset J, Belaidi E, Ovize M, Touret M, Natal S, Mollereau B (2012) ER stress inhibits neuronal death by promoting autophagy. Autophagy 8, 915–926.

Freeman OJ, Mallucci GR (2016) The UPR and synaptic dysfunction in neurodegenerative diseases. Brain Res. 1648, 530–537.

Gallagher CM, Walter P (2016) Caenorhabditis elegans aging. Nat. Rev. Mol. Biol. 17, 158–169.

Gallagher CM, De L’Etang A, Maharanar M, Cordeiro Brana M, Ruegssegger C, Rehmann R, Goswami A, Roos A, Troost D, Schneider BL, Weis J, Saxena S (2015) Marinsco-Schmid syndrome protein SLN1 regulates motor neuron subtype-selective ER stress in ALS. Nat. Neurosci. 18, 227–238.

Ghosh AK, Garg SK, Mau T, O’Brien M, Liu J, Yung R (2015) Elevated endoplasmic reticulum stress response contributes to adipose tissue inflammation in aging. Cell Metab. 21, 158–170.

Hovland C, Ruben L, Helenius A (2003) Quality control in the endoplasmic reticulum. Rev. Mol. Cell Biol. 3, 261–284.

Guileard L, Helenius A (2003) Quality control in the endoplasmic reticulum. Nat. Rev. Mol. Cell Biol. 4, 181–191.

Gavilan MP, Pintado C, Gavilan E, Jimenez S, Rios RM, Vitorica J, Castano A, Ruano BK, Dillin A (2015) Heterotypic signals from neural HSF-1 separate thermotolerance from longevity. Cell 162, 1196–1204.

Hobart CA, Glimcher LH (2009) XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. Proc. Natl. Acad. Sci. USA 106, 14914–14919.

Bernard-Marissal N, Mounen A, Sunyach C, Pellegrino C, Dudley K, Henderson CE, Raoul C, Pettmann B (2012) Reduced calreticulin levels link endoplasmic reticulum stress and Fas-triggered cell death in motoneurons vulnerable to ALS. J. Neurosci. 32, 4901–4912.

Bernard-Marissal N, Sunyach C, Marisal T, Raoul C, Pettmann B (2015) Calreticulin levels determine onset of early muscle degeneration by fast motoneurons of ALS model mice. Neurobiol. Dis. 73, 130–136.

Bettigole SE, Glimcher LH (2015) Endoplasmic reticulum stress in immunity. Annu. Rev. Immunol. 33, 107–138.

Braakman I, Bulleid NJ (2011) Protein folding and modification in the mammalian endoplasmic reticulum. Annu. Rev. Biochem. 80, 71–99.

Brayne C (2007) The elephant in the room – healthy brains in later life, epidemiology and public health. Nat. Rev. Neurosci. 8, 233–239.

Caflon M, Zeng H, Ufaro F, Till H, Hubbard SR, Harding HP, Clark SG, Ron D (2002) Ire1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. Nature 415, 92–96.

Casas-Tinto S, Zhang Y, Sanchez-Garcia J, Gomez-Velazquez M, Rincon-Limas DE, Fernandez-Funez P (2011) The ER stress factor XBP1s prevents amyloid-beta neurotoxicity. Hum. Mol. Genet. 20, 2144–2160.

Castillo V, Onate M, Woelhier B, Ropaz P, Andreu C, Medinas D, Valdes P, Osorio F, Mercado G, Vidal RL, Muffat I, Mitopilava M, Puth M, Ji NT, Schule B, Lasm RA, Tsai LH, Krainc D, Buchwald SL, Jaenisch R, Lindquist S (2013) Identification and rescue of alpha-synuclein toxicity in Parkinson patient-derived neurons. Science 342, 983–987.

Chevet E, Hecz T, Samali A (2015) Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis. Cancer Discov. 5, 586–597.

Choi KM, Kwon YY, Lee CK (2013) Characterization of global gene expression during assurance of lifespan extension by caloric restriction in budding yeast. Exp. Gerontol. 48, 1455–1468.

Chung CY, Khurana V, Auluck PK, Tardif DF, Mazzulli JR, Soldner F, Baru V, Lou Y, Freyzon Y, Cho S, Mungenast AE, Muffat I, Mitopilava M, Puth M, Ji NT, Schule B, Lippard SJ, Tsai LH, Krainc D, Buchwald SL, Jaenisch R, Lindquist S (2013) Identification and rescue of alpha-synuclein toxicity in Parkinson patient-derived neurons. Science 342, 983–987.

Cornevo VH, Pihan V, Pidal RL, Hecz T (2015) Role of the unfolded protein response in organ physiology: lessons from mouse models. IUBMB Life 65, 962–975.

Cui HI, Liu XG, McCormick M, Wasko BM, Zhao W, He X, Yuan Y, Fang BX, Sun XR, Kennedy BK, Suh Y, Zhou ZJ, Kaeberlein M, Feng WL (2015) PmT1 deficiency enhances basal UPR activity and extends replicative lifespan of Saccharomyces cerevisiae. Age (Dordr) 37, 9788.

Douglas PM, Baird NA, Simic MS, Uhlein S, McCormick MA, Wolff SC, Kennedy BK, Dillon A (2015) Heterotypic signals from nervous system-derived neurons in later life, G. Martínez et al. Published by the Anatomical Society and John Wiley & Sons Ltd.

Hetz C (2012) The unfolded protein response: controlling cell fate decisions under stress. Nat. Rev. Neurosci. 13, 89–102.

Hetz C, Mollereau B (2014) Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. Nat. Rev. Neurosci. 15, 1–19.

Hetz C, Thielen P, Matus S, Nassif M, Court F, Kiffin R, Martinez G, Cueno AM, Brown RH, Glimcher LH (2009) XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. Genes Dev. 23, 2294–2306.

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Hetz C, Martinon F, Rodriguez D, Gimlich LH (2011) The unfolded protein response: integrating stress signals through the stress sensor IRE1alp. Physiol. Rev. 91(4), 1197–1219.

Hetz C, Chevet E, Harding HP (2013) Targeting the unfolded protein response in disease. Nat. Rev. Drug Discov. 12, 703–719.

Hetz C, Chevet E, Oakes SA (2015) Proteostasis control by the unfolded protein response. Nat. Cell Biol. 17, 829–838.

Hussain SG, Ramaiah KV (2007) Reduced eIF2alpha phosphorylation and increased neurotoxicity in mammals. J. Neurosci. Res. 85, 488–498.

Kim B, Kim CY, Lee MJ, Joo YH (2009) Preliminary evidence on the association between XBP1-116C/G polymorphism and response to prophylactic treatment with valproate in bipolar disorders. J. Psychiatr. Res. 43, 970–977.

Kannan S, Dawany N, Kurupati R, Showe LC, Ertl HC (2016) Age-related changes with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness. Cell Stem Cell 12, 487–496.

Kouris N, Tavamparasik N (2011) Cellular stress response pathways and ageing: intricate molecular relationships. EMBO J. 30, 2520–2531.

Kozlowski L, Garvis S, Bedet C, Palladino F (2014) The Kondo T, Asai M, Tsukita K, Kutoku Y, Ohsawa Y, Sunada Y, Imamura K, Egawa N, Kim B, Kim CY, Lee MJ, Joo YH (2009) Preliminary evidence on the association between XBP1-116C/G polymorphism and response to prophylactic treatment with valproate in bipolar disorders. J. Psychiatr. Res. 43, 970–977.

Kozlowski L, Garvis S, Bedet C, Palladino F (2014) The Caenorhabditis elegans HPS1 family protein HPL-2 maintains ER homeostasis through the UPR and hormesis. Proc. Natl. Acad. Sci. USA 111, 5956–5961.

Labbadia J, Morimoto RI (2014). Proteostasis and longevity: when does aging really begin? F1000Prime Rep. 6, 7.

Labunsky VM, Gerashchenko MV, Delaney JR, Kaya A, Kennedy BK, Kaerebelien M, Gladyshev VN (2014) Lifespan extension conferred by endoplasmic reticulum secretory pathway deficiency requires induction of the unfolded protein response. PLoS Genet. 10, e1004019.

Leal SL, Yassa MA (2015) Neurocognitive aging and the hippocampus across species. Trends Neurosci. 38, 800–812.

Lee S, Huang EJ (2017) Modeling ALS and FTD with iPSC-derived neurons. Cell Stem Cell 20, 253–266.

Lee K, Tirasophon W, Shen X, Michalak M, Prywes R, Okada T, Yoshida H, Mori K, Court FA (2016) Activation of the unfolded protein response promotes axonal degeneration following peripheral nerve injury. Sci. Rep. 6, 21709.

Morley JF, Morimoto RI (2004) Regulation of longevity in Caenorhabditis elegans by heat shock factor and molecular chaperones. Mol. Biol. Cell 15, 657–664.

Naidoo N, Ferber M, Master M, Zhu Y, Pack AI (2008) Aging impairs the unfolded protein response to sleep deprivation and leads to proapoptotic signaling. J. Neurosci. 28, 6539–6548.

Naidoo N, Davis JG, Zhu J, Yabumoto M, Singleterry K, Brown M, Galante R, Agarwal B, Baur JA (2014) Aging and sleep deprivation induce the unfolded protein response in the pancreas: implications for metabolism. Aging Cell 13, 131–141.

Onate M, Catenaccio A, Martinez G, Armentano D, Parsons G, Kerr B, Hetz C, Court FA (2016) Activation of the unfolded protein response promotes axonal degeneration following peripheral nerve injury. Sci. Rep. 6, 21709.

van Oosten-Hawle P, Morimoto RI (2014a) Organismal proteostasis: role of cell-nonautonomous regulation and transcellular chaperone signaling. Genes Dev. 28, 1533–1543.

van Oosten-Hawle P, Morimoto RI (2014b) Transcellular chaperone signaling: an organismal strategy for integrated cell stress responses. J. Exp. Biol. 217, 129–136.

Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, Tuncman G, Gorgun C, Gimlich LH, Hotamisligil GS (2004) Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 306, 457–461.

Paz Gazvini M, Vela J, Castano A, Ramos B, del Rio VC, Vitorica J, Ruano D (2006) Cellular environment facilitates protein accumulation in aged rat hippocampus. Neurobiol. Aging 27, 973–982.

Plate L, et al. (2016) Small molecule proteostasis regulators that reprogram the ER to reduce extracellular protein aggregation. Elife 5, e15550.

Powaz ET, Balch WE (2013) Diversity in the origins of proteostasis networks—a driver for protein function in evolution. Nat. Rev. Mol. Cell Biol. 14, 237–248.

Riera CE, Dillin A (2015) Tipping the metabolic scales towards increased longevity in mammals. Nat. Cell Biol. 17, 196–203.

Ron D, Walter P (2007) Signal integration in the endoplasmic reticulum unfolded protein response. Nat. Rev. Mol. Cell Biol. 8, 519–529.

Rozas P, Bagsted L, Martinez F, Hetz C, Medinas DB (2016) The ER proteostasis network in ALS: determining the differential motoneuron vulnerability. Trends Neurosci. 39, 9–15.

Rueggerrer C, Saxena S (2016) Proteostasis impairment in ALS. Brain Res. 1648, 571–579.

Safra M, Ben-Hamo S, Kenyon C, Henis-Korenblit S (2013) The ire-1 ER stress-response pathway is required for normal secretory-protein metabolism in C. elegans. J. Cell Sci. 126, 4136–4146.

Santos CK, Tanaka LY, Wosiaki J, Laurindo FR (2009) Mechanisms and implications of reactive oxygen species generation during the unfolded protein response: roles of endoplasmic reticulum oxidoreductases, mitochondrial electron transport, and NADPH oxidase. Antioxid. Redox Signal. 11, 2409–2427.

Scherer W, Hoozemans JJ (2015) The unfolded protein response in neurodegenerative diseases: a neurophathological perspective. Acta Neuropathol. 130, 315–331.
