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Review

The intersection between growth factors, autophagy and ER stress: A new target to treat neurodegenerative diseases?

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ABSTRACT

One of the salient features of most neurodegenerative diseases is the aggregation of specific proteins in the brain. This proteostasis imbalance is proposed as a key event triggering the neurodegenerative cascade. The unfolded protein response (UPR) and autophagy pathways are emerging as critical processes implicated in handling disease-related misfolded proteins. However, in some conditions, perturbations in the buffering capacity of the proteostasis network may be part of the etiology of the disease. Thus, pharmacological or gene therapy strategies to enhance autophagy or UPR responses are becoming an attractive target for disease intervention. Here, we discuss current evidence depicting the complex involvement of autophagy and ER stress in brain diseases. Novel pathways to modulate protein misfolding are discussed including the relation between aging and growth factor signaling.

This article is part of a Special Issue entitled SI:Autophagy.

Contents

1. Protein misfolding disorders

Neurodegenerative diseases are expected to become the second cause of death in the world by 2040 (Fontana et al., 2014; Halliday and Mallucci, 2014). Thus, understanding the biochemical and molecular mechanisms that lead to neurodegeneration and the development of effective therapeutic treatment are needed in the short term. Growing evidence suggests that perturbation of protein homeostasis (referred to as proteostasis) is a salient feature of

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most age-related neurodegenerative diseases (Hetz and Mollereau, 2014; Tanaka and Matsuda, 2014). A variety of brain pathologies, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Huntington's disease (HD) share a common feature, the accumulation of misfolded proteins in both sporadic and familial cases (Hetz and Mollereau, 2014). These disorders are classified as protein-misfolding disorders (PMDs) and are characterized by the accumulation of protein aggregates containing specific proteins including for example, amyloid β (Aβ) peptide or Tau in AD, α-synuclein in PD, mutant huntingtin (Htt) in HD, mutant superoxide dismutase 1 (SOD1) or TDP-43 in ALS, and misfolded prion protein (PrP) in Prion-related disorders (Halliday and Mallucci, 2014). Depending on the context, a combinatory of disease mechanisms may operate in PMDs including oxidative stress, brain inflammation, altered axonal trafficking, excitotoxicity, alterations in RNA metabolism, neuronal connectivity, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, autophagy impairment, among other molecular alterations. Interestingly, impairment of global proteostasis is emerging as a transversal perturbation in most PMDs, where we highlight the occurrence of chronic ER stress (Hetz and Mollereau, 2014) and autophagy impairment (Menzies et al., 2015; Vidal et al., 2014) as common interconnected alterations. In general, most proteins linked to PMDs target different aspects of the secretory pathway, resulting in ER stress. To cope with protein folding stress at the ER, an orchestrated reaction is engaged known as the unfolded protein response (UPR), which modulates diverse processes to restore proteostasis including protein folding and synthesis, ER-associated degradation (ERAD) and autophagy (Hetz, 2012; Walter and Ron, 2011). In the context of aging and the nervous system, a dynamic cross talk between the UPR and growth factor signaling is emerging as a new player linking the proteostasis network with survival signals that also modulate neuronal physiology. This review focuses on discussing the interplay between ER stress, autophagy and growth factors in neurodegenerative diseases and its relevance as a possible target for disease intervention.

2. The core autophagy pathway

Macroautophagy (here referred to as autophagy) is a catabolic process, highly conserved from yeast to mammals, that mediates the recycling of proteins, cytoplasmic components and organelles through lysosome-mediated degradation (Levine and Kroemer, 2008; Mizushima et al., 2008). Autophagy is activated under diverse stress conditions, including nutrient deprivation, operating as a key mechanism to maintain metabolic functions by eliminating damaged organelles and recycling amino acids to maintain protein synthesis and ATP production (Lum et al., 2005). Autophagy is emerging as a relevant factor modulating important cellular processes such as cell survival, cell death, immune responses, development among other events (Levine and Klionsky, 2004; Harris and Rubinsztein, 2012). Autophagy is initiated by the formation of an isolated double membrane termed the autophagosome that engulfs cytoplasmic contents or organelles to be degraded. Then, autophagosomes fuse with the lysosomal membrane forming the autophagolysosome, causing the degradation of its cargo by lysosomal enzymes (Fig. 1) (Mizushima et al., 2010; Rubinsztein et al., 2011).

Autophagy is a multi-step process governed by a family of autophagy-related proteins (ATGs), that can be divided in the following stages: autophagy induction, nucleation/autophagosome formation, vesicle expansion, cargo recognition, fusion with lysosomes, and autophagosome clearance (Wong and Cuervo, 2010). The initiation of the autophagy process is mediated in part by a protein kinase complex that responds to upstream stimuli (ATG/ULK complex), that include nutrient starvation, cellular stress, or reduced availability of growth factors (Efeyan et al., 2015). Among the numerous components involved in the regulation of autophagy, the mammalian target of rapamycin (mTOR) is an essential

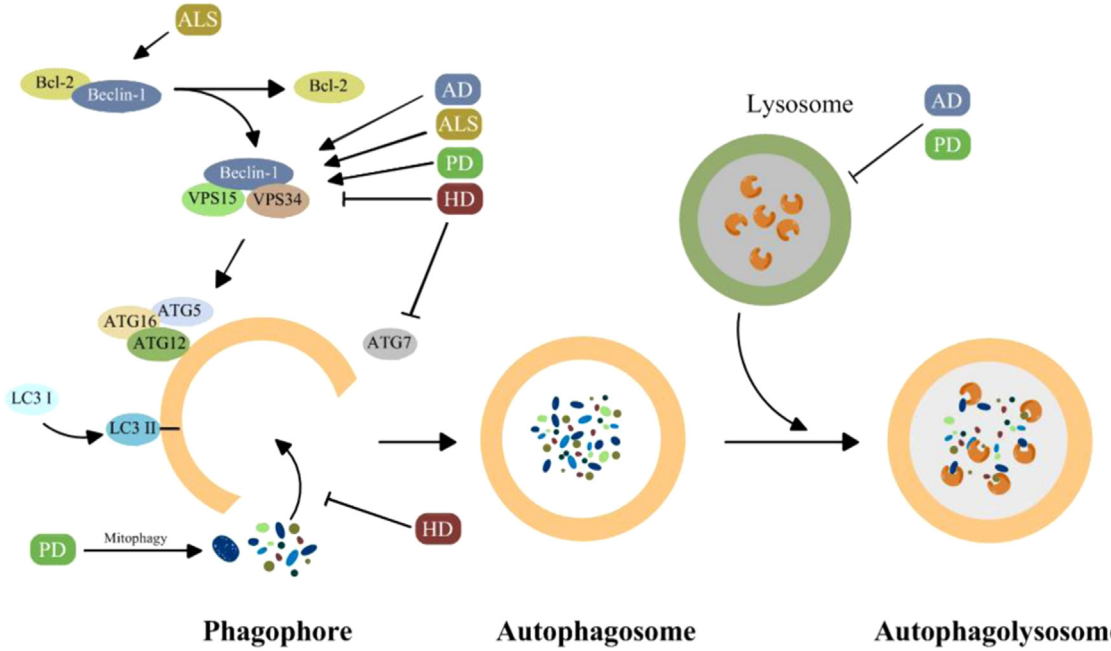

Fig. 1. The autophagy pathway: its regulation and impairment in PMDs. The fundamental components of the nucleation complex are BECLIN1, which is regulated by BCL-2/BCL-X_L, and VPS34. ATG12 and ATG5 are responsible for vesicle expansion, which in association with ATG16, translocate to the membrane of early autophagosomes and promote the conjugation of microtubule-associated protein light chain 3 (LC3) to phosphatidylethanolamine (PE). After LC3-I translocation to the autophagosome membrane, these fuse with lysosomes forming autophagolysosomes, where cargo is degraded. Autophagy failure is an important hallmark of PMDs. HD is associated with cargo delivery impairment, engaged ATG7 expression and nucleation complex sequester. In PD, alterations in mitophagy and nucleation complex formation are reported. Also in AD, abnormal interactions between BECLIN1 and PARKIN complex and alterations in the lysosomal compartment have been described. In ALS, the initiation steps of autophagy may be engaged as mutant SOD1 interacts with BECLIN1/BCL-2 complex.

component that controls the metabolic status of the cell in part as a repressor for autophagy initiation (Jewell and Guan, 2013). However autophagy is also regulated through mTOR-independent mechanisms mediated, for example, by the production of inositols and calcium regulation (Sarkar, 2013). The nucleation and formation of the autophagosome involves the generation of phosphatidylinositol-3-phosphate (PI_3P) through the class III phosphatidylinositol-3-kinase (PI_3K) VPS34, which mediates the localization of other ATG proteins to the pre-autophagosomal structure (Mizushima et al., 2008; Puri et al., 2013). Fundamental components of the nucleation complex are BECLIN1 (BCL-2-interacting protein) and VPS34 (Kroemer et al., 2010; Levine et al., 2008). BECLIN1 is negatively regulated by the anti-apoptotic proteins BCL-2 and BCL-X_L forming a complex at the ER membrane (Pattingre et al., 2005; Castillo et al., 2011). Vesicle expansion is carried out by the covalent conjugation of ATG12 to ATG5, which in association with ATG16, translocates to the membrane of early autophagosomes and promotes the conjugation of microtubule-associated protein light chain 3 (LC3) to phosphatidylethanolamine to form LC3-II. Upon conjugation, LC3-II translocates to the autophagosome membrane. Lastly, autophagosomes fuse their membranes to lysosomes for cargo degradation (Feng et al., 2014).

Table 1
Principal autophagy components affected and the corresponding impaired process in the different PMDs.

Disease	Process	Autophagy components
AD	Autophagy-mediated degradation	Lysosomes (Lee et al., 2010; Yang et al., 2014)
	Nucleation complex	Beclin-1 (Pickford et al., 2008; Lonskaya et al., 2013)
PD	High lysosomal pH	Mutations in ATP13A2 (Dehay et al., 2012)
	CMA, lysosomal pH, vesicular traficcking	LRRK2 mutation (Orenstein et al., 2013; Martinez-Vicente et al., 2008)
	Nucleation complex	Beclin-Parkin (Michiorri et al., 2010)
	Mitophagy	PINK2/Parkin (Youle and Narendra, 2011)
	Vesicle trafickking	VPS35 (Zavodszky et al., 2014)
HD	Vesicle expansion	ATG7 polymorphism (Metzger et al., 2010)
	Altered cargo delivery	Cargo recognition (Martinez-Vicente et al., 2010)
	Nucleation complex	Beclin (Shibata et al., 2006)
ALS	Endosomes formation and cargo delivery	p62, UBQL2 and optineurin (Cirulli et al., 2015)
	Autophagic maturation	TBK1 (Hetz et al., 2007a)
	Nucleation complex	Beclin-1 (Hetz et al., 2007a)

3. Autophagy impairment in PMDs

Autophagy is becoming an interesting target for disease intervention in PMDs since most aggregate-prone proteins linked to PMDs are efficient substrates of autophagy (Rubinsztein et al., 2012). However, accumulating evidence support a new concept where alterations in the autophagy process at different stages may operate as part of the disease mechanisms, affecting the degradation of abnormal proteins and organelles, contributing to neuronal dysfunction and neurodegeneration (reviewed in (Menzies et al., 2015)). Thus, identifying specific defects in the autophagy process is crucial to develop possible therapeutic interventions that aim reestablishing the efficiency of the autophagy process in the brain (Vidal et al., 2014). Several regulatory steps of the autophagy process are disrupted in certain neurodegenerative diseases, where we highlight insufficient autophagy activation, abnormal cargo recognition, reduced lysosomal function or overactivation of the pathway (Harris and Rubinsztein, 2012; Cheung and Ip, 2011).

Genetic inactivation of components involved in vesicle expansion (*Atg5* or *Atg7)* in the central nervous system cause spontaneous neurodegeneration in mice, leading to the accumulation of protein aggregates, extensive neuronal loss and motor impairment (Hara et al., 2006; Komatsu et al., 2006). Interestingly, a genetic study correlated the severity of HD with a polymorphism in *ATG7 (*Metzger et al., 2010*)*. Future studies explaining the functional effect of this polymorphism would be of great importance, since autophagy is the main clearance mechanism for mutant HTT aggregates (Ravikumar et al., 2002). In addition, altered cargo delivery to autophagosome has been reported in HD (Martinez-Vicente et al., 2010). Autophagy impairment has been also proposed as an early event in ALS models during the pre-symptomatic stage (Xie et al., 2015a, 2015b). Mutations in multiple genes encoding for proteins involved in autophagy are linked to the development of ALS including p62, UBQL2, Optineurin and TBK1 (Cirulli et al., 2015). Although alterations in the autophagy pathway are observed in ALS, this catabolic route operates as an mechanism to clear out most common protein aggregates involved in the disease including TDP-43 and SOD1 (Navone et al., 2015) (Fig. 1 and Table 1).

Reduced lysosomal activity is observed in AD models, which may impair autophagy-mediated degradation (Lee et al., 2010; Yang et al., 2014a) (Fig. 1). In fact, restoring lysosomal function in mouse models of AD attenuates the neuropathological process (Yang et al., 2011). Similarly, lysosomal pH is abnormally high in PD patients and mutations on the lysosomal ATPase *ATP13A2* in rare familial cases cause proteolytic failure and an abnormal accumulation of autophagosomes (Dehay et al., 2012). Besides, *LRRK2* mutations in PD have been linked to defects in lysosomal pH, calcium regulation, chaperone-mediated autophagy (Orenstein et al., 2013; Martinez-Vicente et al., 2008) and autophagy vesicular trafficking through interactions with RAB1 (Winslow et al., 2010). Less frequent mutations linked to PD, such as VPS35, may also contribute to autophagy impairment due to altered vesicle trafficking (Zavodszky et al., 2014). Taken together, it is clear that disturbance in the autophagy and the lysosomal pathways contribute to the progression of neurodegenerative disorders (Table 1).

A common molecular alteration in the autophagy pathway in neurodegenerative diseases is the alteration in the function of the BECLIN-1 complex. Many studies have described a functional role of BECLIN-1 in neurodegenerative diseases (Shibata et al., 2006; Pickford et al., 2008; Nassif et al., 2014; Salminen et al., 2013; Pacheco and Lieberman, 2007) and others pathological conditions, such as cancer (Liang et al., 1999; Qu et al., 2003; Yue et al., 2003). In HD, mutant Htt aggregates have been proposed to sequester BECLIN-1, which may result in decreased autophagy activity (Shibata et al., 2006). In the context of ALS we reported a physical interaction between mutant SOD1 and the BECLIN1/BCL-X_L complex that may destabilize this interaction overactivating autophagy (Hetz et al., 2007a) (Fig. 1). Importantly, *BECN1* haplo-insufficiency has a protective effect against experimental ALS, suggesting that autophagy deregulation contributes to the disease process (Nassif et al., 2014). Of note, BECLIN-1 levels or its availability are decreased in normal brains during aging, which correlates with increased vulnerability to the main neurodegenerative diseases such AD (Pickford et al., 2008). Functional studies have shown that the overexpression of BECLIN-1 can protect against neurodegeneration in models of PD and AD (Lonskaya et al., 2013; Michiorri et al., 2010) (Fig. 1), although it has been reported that the Parkin-BECLIN-1 complex is altered in mouse models of AD (Lonskaya et al., 2013). Besides, the PD-related proteins PINK1 and Parkin operate as central components of the mitophagy pathway (Youle and Narendra, 2011). PINK1 increases autophagic functions by direct

interaction with BECLIN-1, and PD-linked mutations in PINK1 cause recessive forms of the disease (Michiorri et al., 2010) (Fig. 1). Thus, PMD-related protein may alter autophagy function through direct interactions with relevant regulators of the pathway (Vidal et al., 2014) (Table 1).

The therapeutic value of autophagy in neurodegenerative diseases has been validated with pharmacological and gene therapy approaches. Several compounds can stimulate the autophagy pathway with a therapeutic gain in multiple animal models of PMDs (Vidal et al., 2014; Rubinsztein et al., 2012). Autophagy induction by rapamycin, an inhibitor of mTOR, provides protective effects in several experimental models of neurodegeneration (Vidal et al., 2014). For example, the administration of rapamycin delays experimental HD (Sarkar et al., 2009; Ravikumar et al., 2004). Rapamycin and mTOR-independent inducers of autophagy can also delay ALS in mouse models based on TDP-43 overexpression (Wang et al., 2012). In contrast, in ALS models triggeted by mutant SOD1 overexpression rapamycin treatment accelerates the disease progression associated with exacerbated apoptosis (Zhang et al., 2011b). However, we have shown that stimulation of mTOR-independent autophagy pathway by administrating trehalose delays ALS progression in mutant SOD1 mice (Castillo et al., 2013), an observation confirmed by other groups (Li et al., 2015; Zhang et al., 2014). Treatment of AD or PD models with rapamycin is also neuroprotective (Spilman et al., 2010; Caccamo et al., 2010, 2011; Malagelada et al., 2010). Overall, most accumulating studies suggest a complex scenario where autophagy may play a dual role in neurodegenerative diseases, where it mediates a “downstream effect” by promoting the degradation of misfolded proteins, whereas it can also operate as an “upstream alteration” contributing to the etiology of the disease by impacting global proteostasis. Furthermore, exacerbated or uncontrolled autophagy may also result in cell death due to the loss of organelle homeostasis (Thorburn, 2014).

4. Crosstalk between ER stress and autophagy in neurodegeneration

The UPR operates as a protective reaction under mild ER stress conditions to reduce the load of unfolded proteins. Three main stress sensors mediate the UPR including double-stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1 (IRE1) (Ron and Walter, 2007). UPR activation induces a rapid and transient translational attenuation that is controlled by PERK through the direct phosphorylation and inhibition of the eukaryotic initiation factor 2α (eIF2α) (Hetz et al., 2015). This phosphorylation event allows the selective expression of activating transcription factor 4 (ATF4), which is involved in the regulation of genes related to apoptosis, autophagy, protein folding, amino acid metabolism and antioxidant responses (Walter and Ron, 2011). IRE1α is an endoribonuclease that upon activation splices the mRNA encoding for X box-binding protein 1 (XBP1), resulting in the expression of a potent transcription factor called XBP1 spliced (XBP1s), in addition to degrade a subset of mRNAs (Hetz et al., in press). Under ER stress, ATF6 traffics to the Golgi apparatus, where it is cleaved by site 1 and site 2 proteases (S1P and S2P), releasing a cytosolic fragment (ATF6f), that operates as a transcription factor for certain UPR-related genes related to ERAD among other pathways (Walter and Ron, 2011).

Several studies have demonstrated a dynamic crosstalk

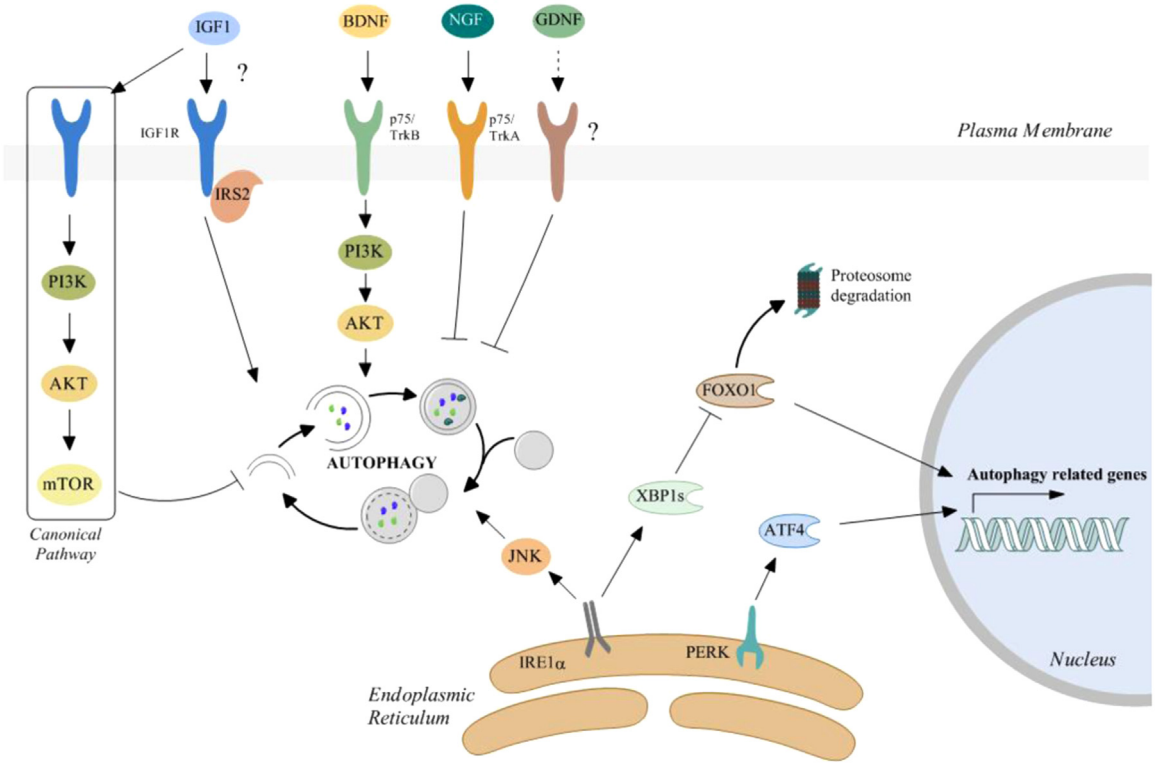

Fig. 2. Autophagy modulation by the UPR and growth factor signaling. Activation of the IGF1R canonical pathway inhibits the autophagy process and its modulation impacts AD, PD and HD progression in experimental models. Signaling mediated by IRS2 enhance autophagy, decreasing mHtt aggregation in HD models. NGF inhibits autophagy through p75 and TrkA in neuron. GDNF deprivation is associated with an increased the number of autophagosomes and autolysosomes and its administration exerts protective effects on the PD models. BDNF promotes neuronal survival and participate in the modulation of autophagy increasing LC3 levels. BDNF signaling has been involved in neuroprotective effect on PMD including AD, HD and schizophrenia. UPR stress sensors regulate autophagy by two distinct mechanisms: promoting the expression of autophagy related genes through IRE1α/XBP1s and PERK/ATF4 signaling or via the signaling of IRE1α/JNK. UPR signaling is involved in benefits effect on ALS, HD and PD through the proteostasis modulation.

between the UPR and autophagy in PMDs. For example, the induction of ER stress by polyglutamine repeats aggregates induce autophagy through the eIF2α pathway (Kouroku et al., 2007) (Fig. 2). ATF4 also transactivates several autophagy-related genes involved in the adaptation to stress including genes implicated in the formation, elongation and function of the autophagosome (B'Chir et al., 2013; Matsumoto et al., 2013; Rzymski et al., 2010) (Fig. 2). This process is regulated in part by the presence of Amino Acid Response Elements (AARE) sequences in the promoter regions of its target genes, allowing the binding of ATF4, CHOP or both (as a heterodimer) (B'Chir et al., 2013).

In general, cell culture studies have suggested that autophagy is enhanced through UPR signaling involving PERK and IRE1, operating as a survival pathway (Hetz et al., 2007b); however the scenario *in vivo* in the context of PMDs is much more complex. In non-neuronal cells, IRE1 signaling has been reported to participate in the connection between the UPR and autophagy in part through the binding of TRAF2 to its cytosolic domain and the activation of downstream JNK (Castillo et al., 2011; Lee et al., 2012; Ogata et al., 2006) (Fig. 2). However, at the preclinical level, the activation of JNK/ASK1 downstream of ER stress and IRE1 has been suggested to enhance apoptosis in models of ALS (Nishitoh et al., 2008). In contrast, we have reported that genetic targeting of *Xbp1* in the nervous system increases autophagy levels, providing protection against experimental ALS (Hetz et al., 2009) and HD (Vidal et al., 2012) due to the clearance of aggregated proteins. Since XBP1 is essential to control the expression of key ERAD genes under stress, such as EDEM1 (Lee et al., 2003), the upregulation of autophagy in XBP1 deficient animals may represent a backup mechanism to compensate the reduction on ERAD activity (Hetz et al., 2009). In fact, autophagy has been referred to as ERAD-II in other systems when ERAD activity or the delivery of substrates to this pathway is impaired (Fujita et al., 2007). In addition, XBP1 may repress autophagy through a negative regulation of the transcription factor FOXO1 (Vidal et al., 2012), an important regulator of autophagy genes in neurons (Vidal and Hetz, 2012; Zhao et al., 2013) (Fig. 2). In models of AD in *C. elegans*, knocking down XBP1 also protects against amyloid β toxicity possibly through the upregulation of autophagy (Safra et al., 2013). Interestingly, in this organism the overactivation of IRE1α and mild ER stress due to XBP1 deficiency was suggested to drive autophagy induction (Safra et al., 2013). Besides, XBP1 has been connected to autophagy inhibition by the control of genes involved in protein acetylation inside the ER (Pehar et al., 2012). On the other hand, induction of mild ER stress with pharmacological agents provides protection against neurodegeneration due to autophagy induction in fly and mouse models of PD through an "hormesis" mechanism (Matus et al., 2012) (Table 2).

Taken together, these few examples support a complex scenario where UPR signaling converges in the modulation of autophagy process at both the transcriptional and posttranslational level suggesting a dynamic interplay between both pathways to maintain global proteostasis (Antonucci et al., 2015). It is becoming evident that depending on the disease context, the crosstalk between the UPR and autophagy pathways may have distinct consequences in cell fate control (Lee et al., 2015; Yang et al., 2010).

5. Aging, growth factor signaling and proteostasis control in PMDs

Aging is the mayor risk factor to develop neurodegenerative diseases. A hallmark of aging is the progressive loss of proteostasis control associated with an attenuated capacity to engage adaptive responses including the UPR and autophagy (Mardones et al., in press) Importantly, accumulating observations in model organisms indicate that aging-related signaling pathways (i.e. insulin and FOXO) are strong proteostasis enhancers (Douglas and Dillin, 2010). In *C. elegans* aging is associated with a dramatic reduction in their response to ER stress, reflected in low XBP1s activity (Ben-Zvi et al., 2009). In this model, genetic inactivation of the UPR reduces the lifespan of worms, associated with altered insulin-like growth factor signaling (Henis-Korenblit et al., 2010). Remarkably, artificial overexpression of XBP1s in neurons in that model organism prolonged life span through a cell-nonautonomous effect (Taylor and Dillin, 2013). These studies suggest that proteostasis alterations in neurons are key factors driving the aging process.

Nutrient deprivation and the withdrawal of growth factors are well-known inducers of autophagy (Jewell and Guan, 2013; Mitchener et al., 1976; Russell et al., 2014). The canonical pathway that regulates mTORC1 involves a delicate regulation through the IGF1/PI_3K-Akt pathways, which negatively regulates autophagy induction (Jia et al., 2006; Sandri, 2008; Jung et al., 2010) (Fig. 2). Changes in the levels of several neuronal growth factors and neurotrophins are frequently observed in PMDs (Lahiri, 2008; Hennigan et al., 2007; Dawbarn and Allen, 2003). For example, the expression of insulin, insulin growth factor 1 and 2 (IGF1 and IGF2), IGF's receptors and downstream substrates are reduced in the brain of AD patients (Carro et al., 2006, 2002; De Felice et al., 2009; Freude et al., 2009; Talbot et al., 2012). Moreover, alterations to insulin and IGF1 signaling progress with the severity of AD (de la Monte, 2012). Also, a correlation between ER stress and IGFs alterations has been proposed in AD (de la Monte et al., 2012). Treatment of AD mouse models with insulin and/or IGF1-based therapies has been shown to protect neurons against amyloid β-

Table 2
Summary of main UPR effectors and growth factor and their involvement in the PMDs.

Disease	UPR signaling involvement	Growth factor involvement
AD	Knocking down XBP1 protects against amyloid β-toxicity (Safra et al., 2013).	Insulin/IGF1 protect neurons against amyloid β-induced neurotoxicity (Carro et al., 2006, 2002; De Felice et al., 2009; Freude et al., 2009; Mellott et al., 2014).
		Insulin, IGF1, IGF2, their receptors and downstream substrates are reduced (Carro et al., 2006; Carro et al., 2002; De Felice et al., 2009; Freude et al., 2009; Talbot et al., 2012).
	Correlation between ER stress and IGF alterations (de la Monte et al., 2012).	IGF2 administration reduces the load of amyloid plaques (Pascual-Lucas et al., 2014).
		BDNF protects against AD (Nagahara et al., 2009).
PD	Induction of mild ER stress provides protection against neurodegeneration due to autophagy induction (Matus et al., 2012).	Treatment of neurons with IGF1 protects cells against 6-OHDA and reduces the levels of α-synuclein aggregation (Guan et al., 2000; Kao, 2009; Krishnamurthi et al., 2004).
		Polymorphism in *IGF2* gene is linked to PD (Sutherland et al., 2008).
HD	*Xbp1* provides neuroprotection (Vidal et al., 2012).	Activation of the IGF1/AKT pathway protects neurons by increased clearance of mutant HTT by autophagy (Humbert et al., 2002; Yamamoto et al., 2006).
	IRE1 participates in ER stress-mediated mutant HTT aggregation and neurotoxicity (Lee et al., 2012).	IGF1R depletion enhanced the accumulation of mHTT protein (Renna et al., 2013).
		BDNF protects against HD (Gauthier et al., 2004).
ALS	JNK/ASK1 IRE1 enhances apoptosis (Nishitoh et al., 2008).	IGF1 delivery delays disease onset and progression (Kaspar et al., 2003).
	Xbp1 provides neuroprotection (Hetz et al., 2009).	VGF delays ALS progress.

induced neurotoxicity, enhancing memory performance of preclinical models of the disease (Carro et al., 2006, 2002; De Felice et al., 2009; Freude et al., 2009; Mellott et al., 2014). Interestingly, administration of IGF2, and not IGF1, to AD models reduces the load of amyloid plaques in the brain (Mellott et al., 2014; Pascual-Lucas et al., 2014). In contrast, genetic inactivation of IGF1 on a different study delayed AD associated with reduced levels of amyloid beta plaques (Cohen et al., 2009) (Table 2). A polymorphism in *IGF2* gene is linked to PD and IGF2 levels are changed in the serum of patients (Sutherland et al., 2008) and also during aging (Fu et al., 2008). In agreement with this observation, the impairment of insulin/IGF1 signaling has been also linked to α-synuclein aggregation (Guan et al., 2000; Kao, 2009; Krishnamurthi et al., 2004) and ER stress in PD models (Kim et al., 2012; Sun et al., 2010). Depletion of IGF1 receptor enhanced the accumulation of mutant Htt protein (Renna et al., 2013). In ALS, gene therapy based on the delivery of IGF1 has dramatic effects on delaying disease onset and progression (Kaspar et al., 2003). In contrast, IGF1 signaling in *C. elegans* increased TDP-43 aggregation (Zhang et al., 2011a) (Table 2). Thus, increasing evidence links IGF signaling with PMDs and proteostasis alterations.

We recently uncovered a novel role of XBP1 in the physiology of the nervous system, where it controls learning and memory-related processes (Martínez et al., in press). This novel activity of XBP1 in the brain involves the transcriptional regulation in the hippocampus of brain-derived neurotrophic factor (BDNF), a key factor driving neuronal plasticity and memory consolidation (Lu et al., 2008). Moreover, BDNF signaling has been show to engage IRE1 activation, enhancing neurite outgrowth (Hayashi et al., 2007), suggesting a bidirectional regulation. BDNF expression protects against a variety of brain diseases including AD (Nagahara et al., 2009), HD (Gauthier et al., 2004) and schizophrenia (Pandya et al., 2013) among others (Nagahara and Tuszynski, 2011; Lu et al., 2013). In this context, BDNF levels negatively correlates with the load of amyloid plaques in the brain (Peng et al., 2009; Tapia-Arancibia et al., 2008; Budni et al., 2015). Moreover, BDNF can enhance neuronal survival via the upregulation of autophagy in certain experimental systems (Chen et al., 2013; Yang et al., 2014) (Fig. 2). However, the link between BDNF signaling and autophagy has been only described in environmental enrichment paradigms and in the aging brain (Yang et al., 2014b; Takahashi et al., 2014) and further studies are needed to better define the impact of BDNF to PMDs (Table 2).

Although most of the studies linking autophagy with growth factors involve IGF1, other neurotrophic factors can also modulate the pathway. Nerve growth factor (NGF) is capable to modulate autophagy process (Florez-McClure et al., 2004). Glial cell line-derived neurotrophic factor (GDNF) has also potent neuroprotective effects on diverse conditions (Lin et al., 1993; Tomac et al., 1995; Henderson et al., 1994). GDNF deprivation increases autophagy suggesting that its protective effects may be due in part to improved proteostasis (Yu et al., 2003) (Fig. 2). In other studies, GDNF did not have any effect on a genetic model of PD based on α-synuclein expression (Decressac et al., 2011). Other growth factors such as vascular growth factor (VGF) attenuate ER stress and disease progression in ALS. In summary, the crosstalk between growth factors and the proteostasis machinery (i.e. autophagy and the UPR) are emerging as relevant factors modulating neurodegenerative conditions (Table 2).

6. Concluding remarks

Proteostasis alterations are a hallmark of most prevalent neurodegenerative diseases. Currently, increasing evidence supports the idea that manipulation of neuronal proteostasis at the level of autophagy or ER stress signaling has significant effects in delaying neurodegeneration in experimental models of PMDs. However, the underlying mechanisms that led to proteostasis impairment during aging and its link to degeneration is poorly defined. Future studies should focus on defining the nature of the proteostasis defects, the cellular responses associated with these alterations and functional consequences on disease progression in the context of aging.

In this review we have discussed the emerging role of autophagy and ER stress to neurodegeneration and its possible link to some growth factors. A close homeostatic crosstalk between both stress pathways is emerging as a relevant *hormesis* mechanism of protection that could be exploited for disease intervention. Growth factor signaling may play an important role in enhancing autophagy, in addition to engage other relevant pro-survival effects that fine tune the proteostasis network. We propose that gene therapy strategies focused on the delivery of growth factors in the brain may have interesting pleiotropic effects in bursting the proteostasis capacity of the cell (i.e. autophagy and the UPR), in addition to enhance other relevant process related to synaptic plasticity, neuronal survival and function. We speculate that combinatorial therapies aiming restoring autophagy capacity, reducing ER stress and enhancing prosurvival signaling may represent an interesting concept for future success in therapeutic development.

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