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Review

Endoplasmic reticulum, oxidative stress and their complex crosstalk in neurodegeneration: proteostasis, signaling pathways and molecular chaperones

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Abstract: Cellular stress caused by protein misfolding, aggregation and redox imbalance is typical of neurodegenerative disorders such as Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS). Activation of quality control systems, including endoplasmic reticulum (ER)-mediated degradation, and reactive oxygen species (ROS) production are initially aimed at restoring homeostasis and preserving cell viability. However, persistent damage to macromolecules causes chronic cellular stress which triggers more extreme responses such as the unfolded protein response (UPR) and non-reversible oxidation of cellular components, eventually leading to inflammation and apoptosis. Cell fate depends on the intensity and duration of stress responses converging on the activation of transcription factors involved in the expression of antioxidant, autophagic and lysosome-related genes, such as erythroid-derived 2-related factor 2 (Nrf2) and transcription factor EB respectively. In addition, downstream signaling pathways controlling metabolism, cell survival and inflammatory processes, like mitogen activated protein kinase and nuclear factor-kB, have a key impact on the overall outcome.

Molecular chaperones and ER stress modulators play a critical role in protein folding, in the attenuation of UPR and preservation of mitochondrial and lysosomal activity. Therefore, the use of chaperone molecules is an attractive field of investigation for the development of novel therapeutic strategies and disease-modifying drugs in the context of neurodegenerative diseases such as PD and ALS.

Keywords: Parkinson's Disease; Amyotrophic Lateral Sclerosis; endoplasmic reticulum; oxidative stress; MAPK; NFkB; autophagy; molecular chaperones

1. Introduction

Cellular stress is a mechanism of critical (patho)physiological significance and is generally accompanied by stress-induced responses. Many aspects of the cellular stress response are not specific because they depend on the macromolecular damage without regard to the type of trigger [1]. Also, these responses converge, interact and ultimately determine the fate of the stressed cell: either survival or death. The final impact on cell viability largely depends on the nature and duration of the stress as well as the cell type. Among cell stress inducers, protein misfolding and aggregation, overload of endoplasmic reticulum (ER) and reactive oxygen species (ROS), responsible for the onset of ER stress and oxidative stress (OS) respectively, are critical players in several neurological disorders including neurodegenerative diseases, such as Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS) [2,3].

PD is the second most prevalent neurological disorder affecting approximately 1% of the population in the age of sixties [4]. PD is caused by gradual reduction of dopamine and progressive dopaminergic neuron loss in the substantia nigra pars compacta (SNc), a midbrain area within the basal ganglia. From a clinical perspective, PD is mainly characterized by impaired motor performance, however non-motor symptoms such as gastrointestinal and sensory symptoms, autonomic dysfunction, sleep and neuropsychiatric disorders and cognitive decline are also reported [5]. Although aging is the main risk factor, PD pathogenesis is based on a complex combination of genetic traits and environmental components [6]. The pathology is strongly associated with protein aggregation, impaired clearance capacity and deposition of insoluble protein aggregates, namely Lewy bodies (LB) which are typical histopathological hallmarks of PD, mainly composed of α-synuclein (α-syn) [7], together with ubiquitin and chaperone proteins. Aggregation of α-syn is dependent on gene (*SNCA*) aberrations as well as micro-environmental factors such as oxidation, metal ions, pesticides, lipids, pH and chaperones availability [8,9].

Together with aggregation-prone α-syn, PD is associated to genes functionally linked to oxidative stress control such as *PARK7* encoding for DJ-1 protein [10], and to protein quality control such as *PARK2*, *PARK5* and *PARK9*, respectively encoding for E3-ubiquitin ligase parkin, ubiquitin carboxyl-terminal esterase L1 (UCHL1) and the lysosomal membrane protein ATP13A2. Finally, even in sporadic PD, the main genetic susceptibility factor known up to date is *GBA* gene, which encodes for the lysosomal enzyme glucocerebrosidase [11-14].

ALS is a neurodegenerative disease characterized by loss of both upper and lower motor neurons in the motor cortex, brainstem and spinal cord. Motor neuronal degeneration leads to muscular atrophy, weakness and ultimately death, primarily caused by respiratory failure, within 2–5 years of symptom onset. Approximately 10% of ALS patients present familial clustering (FALS), and 75% of these familial cases have known mutations in genes with Mendelian transmission [15]. The remaining cases are sporadic (SALS), with no family history. SALS and FALS are clinically very similar and study of the hereditary form of the disease has provided important insights into the molecular understanding of the key pathomechanisms of the sporadic form.

To this regard, the first contribution toward an understanding of ALS pathogenesis has come from the discovery of mutations in the gene encoding the Cu/Zn superoxide dismutase protein or

SOD1, which account for more than 20% of FALS cases [16]. Mutations in SOD1 cause the protein to misfold and aggregate.

Other proteins causing FALS, such as TAR DNA binding protein-43 (TDP-43) and fused in sarcoma (FUS) have also been identified as major constituents of cytoplasmic aggregates in SALS [17-19]. It is noteworthy to mention that FALS is also caused by mutations in genes directly involved in protein clearance and quality control pathways. These include vesicle-associated membrane protein-associated protein B (*VAPB*) [20]; charged multivesicular body protein 2B or chromatin modifying protein 2B (*CHMP2B*) [21]; ubiquilin-2 (*UBQLN2*) [22]; vasolin-containing protein (*VCP*) [23]; optineurin (*OPTN*) [24]; p62/sequestosome (*SQSTM1*) [25-27].

2. Oxidative stress in PD and ALS

OS originates from an imbalance between the production of ROS and the ability of the antioxidant systems to remove oxidizing agents and/or repair the resulting damages to cellular components, such as nucleic acids, proteins, carbohydrates, and lipids. The primary and continuous source of ROS within the cells is the energetic aerobic metabolism occurring in the mitochondria, which consumes 85–90% of total oxygen. Under normal conditions, approximately 2% of electrons leak from the mitochondrial electron transport chain and cause the formation of O_2^- [28]. ROS scavenging is paramount for cell viability and is achieved by the highly coordinated activity of antioxidant defense systems (catalases, peroxidases, superoxide dismutases, glutathione reductases and peroxiredoxins, glutathione, ascorbate, vitamin E and ubiquinol). Low/moderate levels of ROS exert important roles as mediators of normal processes, including signaling events controlling cell proliferation, survival and migration, fine-tuned modulation of gene expression and inflammatory responses. However, ROS overload triggers high deleterious injuries to cell structures. Specifically, ROS can react with polyunsaturated fatty acids causing lipid peroxidation, consequently affecting membrane integrity and cell viability. Typical markers of lipid peroxidation are highly reactive molecules such as 4-hydroxy-2-trans-nonenal (4-HNE), malondialdehyde, acrolein and thiobarbituric acid reactive substances (TBARS) [29]. ROS also attack DNA causing single- and double-strand breaks in DNA backbone and alterations of purine and pyrimidine bases. Furthermore, ROS damage protein backbone and amino acid side chains, thus leading to conformational changes and instability, with consequent impairment of functional structures and enhanced formation of harmful protein oligomers and aggregates. In this context, the efficient removal of the oxidatively damaged and misfolded proteins mediated by the Ubiquitin Proteasome System (UPS) is of critical importance, as it may prevent/limit the formation and/or propagation of toxic insoluble inclusions.

It has been suggested that neurons are particularly sensitive to OS and the involvement of OS in neurodegenerative diseases is well documented [30-36].

Markers of oxidation have been frequently detected in bio-specimens from PD subjects, including autoptic brain tissues, biological fluids and peripheral cells. Raised levels of TBARS and protein carbonyls were found in frontal cortex samples from PD patients in comparison with controls [37]. Levels of 8-OHdG (a marker of DNA damage) were significantly increased in SNc and in CSF and serum from PD patients [38-40]. Increased Coenzyme Q10 oxidation was also observed in CSF from PD subjects [41]. Glutathione oxidation was higher in blood cells while catalase activity was decreased in blood cells from PD patients [42].

Similarly, several studies indicate that OS is involved in ALS. Indeed, multiple markers of

oxidation have been reported in both nervous and peripheral tissues from familial and idiopathic cases [43-45]. These include raised number of oxidized lipids in motor neurons and glial cells from SALS patients when compared to neurologically normal patients, enhanced protein carbonylation and nitration and high levels of 8-OHdG in motor cortex and spinal cord from FALS and SALS. ROS over-expression was detected also in lymphoblasts from SOD1-mutated patients as well as from peripheral blood mononuclear cells from SALS patients when compared to healthy individuals [46-52], which was accompanied by increased SOD1 gene expression and protein aggregation [53,54]. Furthermore, concentration of 4-HNE [55], 8-OHdG and ascorbate free radical [56] was higher in cerebrospinal fluid of FALS and SALS subjects than control groups.

Notably, impairment in antioxidant systems, such as Nrf2/ARE pathway, was reported in both PD and ALS [33,57-60].

3. Endoplasmic reticulum stress and the unfolded protein response in PD and ALS

The ER is a membrane-bound organelle specialized for the folding and post-translational maturation of almost all membrane proteins and most secreted proteins. ER plays an essential role in lipid biosynthesis, detoxification, energy metabolism, homeostasis of intracellular calcium (Ca^{2+}) and redox balance. The ER is responsible for the synthesis and folding of several cellular proteins [61].

The ER is highly susceptible to cellular stress due to several different phenomena such as saturation of ER membrane lipids and therefore ER lipid-bilayer stress, protein aggregation, glucose and oxygen deprivation, increased OS and disrupted intracellular Ca^{2+} balance. These conditions lead to a phenomenon called ER stress responsible for the activation of the ER-associated degradation (ERAD) which involves the ubiquitination of misfolded proteins and their UPS-mediated clearance in the cytosol. If the misfolded protein load becomes excessive and persistent, chronic ER stress activates the unfolded protein response (UPR), which is mediated by three different membrane-associated ER proteins acting as stress sensors [62]. Specifically, the three converging UPR mediators are (i) PKR-like ER kinase (PERK), (ii) inositol requiring kinase 1 (IRE1) and (iii) activating transcription factor 6 (ATF6); these mediators are co-activated and cooperate with the aim of restoring cellular homeostasis through the attenuation of protein synthesis and activation of the transcription of genes involved in protein folding (i.e. chaperones) or degradation (Figure 1).

Despite UPR is activated to play a protective role and support ER function, prolonged UPR leads to the activation of apoptotic and inflammatory pathways. Indeed, the involvement of ER stress and UPR in the pathogenesis of neurodegenerative diseases is gaining growing interest despite its role is still matter of investigation.

UPR activation in neurodegenerative diseases is mainly driven by protein misfolding, aggregation and accumulation through several mechanisms (Figure 2): (i) mutant pathogenic proteins can accumulate in the ER and trigger ERAD; (ii) aggregates of mutant pathogenic proteins (e.g. α-syn) can sequester chaperones and other mediators of protein folding in the ER [63,64]; (iii) aggregates of mutant pathogenic proteins (e.g. SOD1) can target and thereby alter ERAD components or inhibit mediators involved in membrane fission/fusion and ER-Golgi trafficking [65,66]; (iv) disease-linked mutations or aggregates of mutant pathogenic proteins can directly interfere with UPR or perturb ER Ca^{2+} homeostasis through mechanical interaction with channels, pumps and other Ca^{2+}-related receptors (as reviewed in [67]).

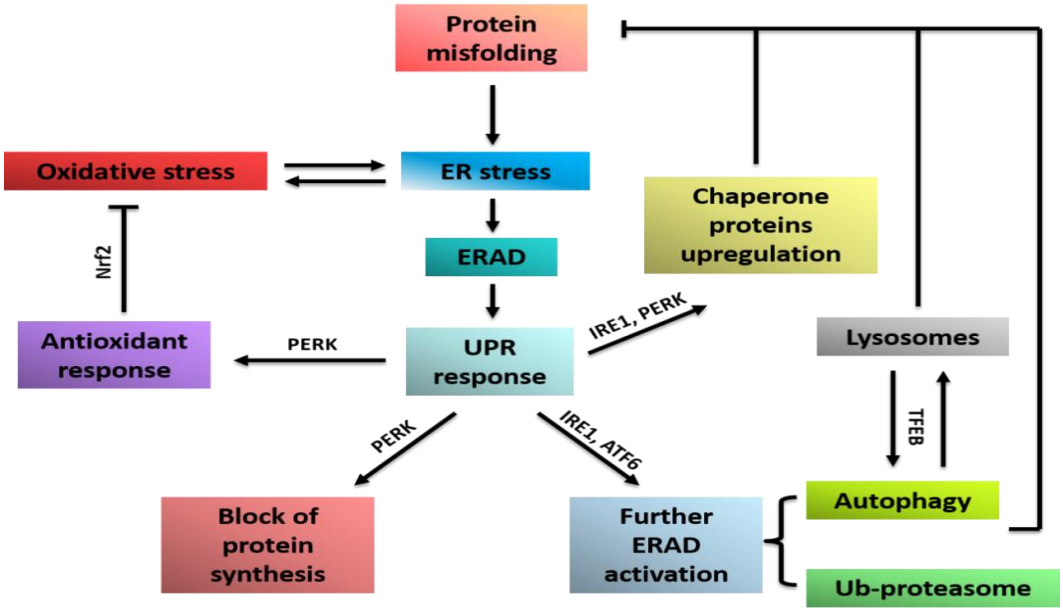

Figure 1. Persistent ER stress induces ERAD and finally the UPR, resulting in the activation of PERK, IRE1 and ATF6. PERK responds to ER stress by phosphorylating eIF2α, which rapidly decreases protein translation thereby reducing ER protein-folding burden. Activated PERK also phosphorylates nuclear factor erythroid-derived 2-related factor 2 or Nrf2, promoting the transcription of antioxidant genes. IRE1 is a kinase that also possesses endonuclease activity. By modulating mRNA splicing, IRE1 promotes the synthesis of the active isoform of X-box binding protein 1 (XBP1), a transcriptional factor which increases the expression of ER chaperones and proteins involved in ERAD and lipogenesis. Finally, activated ATF6 is cleaved in the Golgi and the released cytosolic fragment is responsible for further activating XBP1 as well as ERAD-associated proteins. Therefore, UPR leads to protein synthesis attenuation, gene expression changes, in particular of antioxidant genes via Nrf2, ERAD activation and protein chaperones up-regulation. Lysosomal-autophagic gene expression is supported by transcription factor EB (TFEB) activation.

Whether UPR has a beneficial or detrimental role in PD is not entirely clear; it is likely that the phase of disease progression is essential to determine the final outcome of ER stress-induced responses [68]. In human samples from PD patients, ER stress markers co-localize with α-syn-positive inclusions [69,70]. Other studies unraveling the functional link between UPR and PD pathogenesis are mostly mechanistic and focus on the connection between ER stress and PD-associated genes (as reviewed in [68]), mitochondrial dysfunction and oxidative stress as well as components of the dopaminergic system and dopamine-based neurotransmission [71-73]. In a recent review paper, Mercado et al. discuss the functional contribution of the three branches of the UPR on PD pathophysiology. As for the neuroprotective ATF6-dependent branch, the authors report that loss of nigral dopaminergic neurons is increased in ATF6-deficient mice exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin commonly used to reproduce PD pathology in rodents. They also indicate the ability of α-syn to reduce ATF6 availability in the nucleus through indirect incorporation in vesicles or direct sequestration in the cytosol. ATF6

depletion might be therefore responsible for the activation of apoptotic cascades and cell death. As for the IRE1α/XBP1, the authors highlight a varied effect of this branch modulation in the nigro-striatal circuit, dependent on the developmental stage of the animals. In fact, XBP1 ablation during development would reduce, while down-regulation in adult mice would increase, susceptibility of dopaminergic neurons to neurotoxic insults. Finally, as for the PERK/ATF4 branch, the authors indicate a more complex role. In particular, the authors indicate that the PERK/CHOP (see paragraph 4.1)-induced, block of protein translation might be a critical mechanism promoting neuronal dysfunction and death, not only in PD, but also in other neurodegenerative disorders [74].

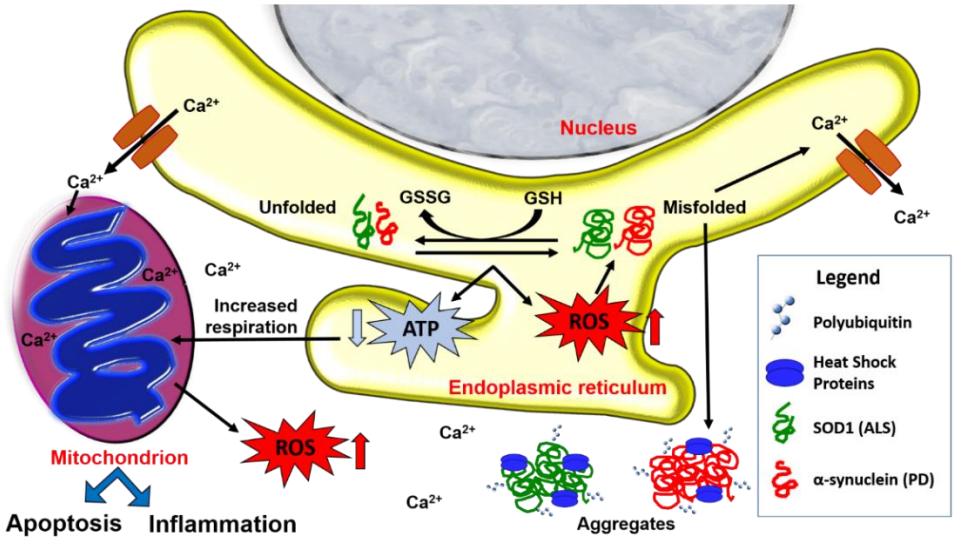

Figure 2. OS and ER stress affect and sustain each other in PD and ALS. Mutant α-syn and SOD1 are folded in the ER. Irreversibly misfolded α-syn and SOD1 form aggregates together with ubiquitin and heat shock proteins thereby causing ER stress. Protein folding in the ER exacerbate OS by (i) exploiting the mitochondrial-driven electron flux (ii) depleting the pool of reduced glutathione. OS promotes ER stress by inducing ER oxidation, by increasing the misfolded protein burden in the ER and impairing ER calcium buffering capacity. Altogether, protein aggregates accumulation, ROS formation and increased calcium levels in the cytoplasm affect mitochondrial function and activate pro-apoptotic and pro-inflammatory processes.

In parallel, ER stress and UPR have been identified as early events in the development of both genetic and sporadic forms of ALS in both animal model of disease and patient-derived spinal cord tissue [75], however non-homogeneous results have been collected on the beneficial or detrimental function of the UPR in ALS development [76,77].

4. Crosstalk between OS and ER stress.

There is a critical interaction and reciprocal crosstalk between OS and ER largely due to the physical connection between ER and mitochondria. The existence of structures known as mitochondria-associated membranes or MAMs enables a continuous communication between the two organelles with the aim of

maintaining cell homeostasis by promoting efficient and prompt responses to stressing conditions [78]. Especially in the context of neurodegenerative disorders such interaction is critical to control Ca^{2+} fluxes, metabolism, intracellular signaling and ROS production and proteostasis [79].

Mitochondrial ROS and reactive nitrogen species can exacerbate ER stress by affecting the activity of ER chaperones and increasing ER Ca^{2+} release. ER chaperones inhibition impairs protein folding and causes misfolded protein retention in the ER, which further increase ER Ca^{2+} leak. Increased cytosolic Ca^{2+} and Ca^{2+} entry via MAM channels force and overwhelm mitochondrial Ca^{2+}-buffering capacity. Ca^{2+} overload in the mitochondria contribute to membrane depolarization, disruption of electron transport chain activity, cytochrome c release and further ROS production (Figure 2). Through this vicious cycle, Ca^{2+} release, ROS and protein misfolding activate Ca^{2+}-dependent kinases, such as c-Jun amino-terminal kinases (JNK1/2/3) and nuclear factor-kB (NFkB), leading to pro-apoptotic responses and inflammation [80,81].

On the other hand, ER stress promotes the generation and accumulation of intracellular ROS, since protein folding in the ER is an energy-consuming process that requires oxidizing conditions for the formation of intra and intermolecular disulphide bonds [82]. The formation of disulphide bonds of proteins in the ER is driven by the redox chaperones ER resident protein 57 (ERp57) and protein disulphide isomerase (PDI) as well as other enzymes such as ER oxidoreductin 1 (ERO1) which ensure a robust driving force for disulphide-bond formation. This process, however, leads to ROS production, hydrogen peroxide in particular. Moreover, extra OS during disulphide bonds formation can be derived from the oxidation of reduced glutathione, whose role is to correct improperly formed disulphide bonds [83]. Therefore, over-loading the protein folding processes in the ER can lead to ROS accumulation. Interestingly, upregulation of PDI was detected, in cellular models of PD as well as cellular and animal models of ALS. Furthermore, mutant variants of both ERp57 and PDI have been associated to ALS, thereby supporting the importance of further investigating these and other redox chaperones as potential therapeutic targets in neurodegeneration [84,85].

- *OS and ER stress converge on signaling pathways to determine cell survival or death.*

As described above, during protein overload, ROS are generated from the electron transfer in the ER as part of the oxidative folding process. ROS can target ER-resident proteins and promote Ca^{2+} release from the ER into the cytosol and to mitochondria. The increased protein folding demand, mitochondrial Ca^{2+} and ROS signaling integrate with UPR pathways and can potentially lead to activation of cellular death programs and inflammatory responses [86].

C/EBP-homologous protein (CHOP) is one major factor whose expression is triggered, among other mechanisms, by ER stress. CHOP contributes to the expression of pro-apoptotic genes –along with UPR [61].

CHOP can inhibit pro-survival protein Bcl-2 through transcriptional suppression and increases expression of cell surface death receptor 5 (DR5) on which, according to Lu et al [87-89], multiple opposing UPR signals converge in order to switch from the activation of adaptive to pro-apoptotic processes.

Furthermore, CHOP can exacerbate OS by promoting protein synthesis during UPR as well as hyper-oxidation of the ER through increased expression of ERO1α and release of Ca^{2+} from the ER [90,91].

Together with CHOP, UPR and OS activate and dictate cell fate through different signaling pathways including mitogen-activated protein kinase (MAPK), NFkB, glycogen synthase kinase 3 (GSK3) (Figure 3), as well as through the modulation of the autophagy-lysosomal homeostasis which is partly linked to transcription factor EB (TFEB)-activated gene expression.

Examples in the context of PD and ALS are reported in Table 1 [92-95].

Table 1. Studies showing association between signaling pathways, OS and ER stress in PD and ALS

UPR and target signaling pathways interaction	Model and effect	Disease	Reference
JNK	Activation of paraquat-induced apoptosis in SH-SY5Y through the activation of IRE1/ASK1/JNK pathway	PD	PMID:19735704
	Activation of IRE1/ASK1/JNK pathway in various models of neurodegenerative disorders	PD, ALS, Huntington's disease	PMID:16472116
GSK3	6-OHDA triggers ER stress and promotes apoptosis through the activation (i.e. de-phosphorylation) of GSK3β(Ser9) in different cellular models (SH-SY5Y and PC12)	PD	PMID:15132987
NFkB	ER stress and expression of NFkB are enhanced in SOD1(G93A) cellular models	ALS	PMID:24666819
TFEB	Chemical chaperone ambroxol reduces OS and activates lysosomal biogenesis/clearance in fibroblasts derived from patients with *GBA* mutations	PD	PMID:24574503
		Gaucher's disease	PMID:26094596

(1) MAPK pathway

MAPK signaling pathways function as modulators for differentiation, proliferation, cell death, and survival by phosphorylating cytosolic or nuclear target proteins and modulating transcription factors activation. MAPKs are divided in three main groups: ERK1/2, JNK1/2/3, and p38 kinases. Commonly, the activation of ERK1/2 has been linked to cell survival, whereas those of JNK and p38 have been associated with apoptosis [96]. OS and ER stress as well as Ca^{2+} homeostasis are the major mediators of MAPK pathway activation, with cell survival or death as possible consequences.

Among UPR mediators, both IRE1 and the PERK-CHOP axis are linked to MAPKs activation, especially JNK and p38 pathways. Persistent induction of IRE1 triggers both JNK and p38 signaling. Activated oligomerized IRE1 interacts with tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF2), which activates apoptosis signal-regulating-kinase 1 (ASK1) and eventually JNK and p38-triggered apoptotic cascades.

While IRE1 activation is sufficient to independently trigger JNK and downstream pro-apoptotic pathways, the PERK-induced CHOP up-regulation indirectly activates JNK and promotes cell death

by exacerbating protein load, OS, energy depletion and promoting ER Ca^{2+}-release. Intriguingly, CHOP is substrate for p38, indicating the existence of a feed-back loop sustaining the lethal branch of MAPK signaling [97].

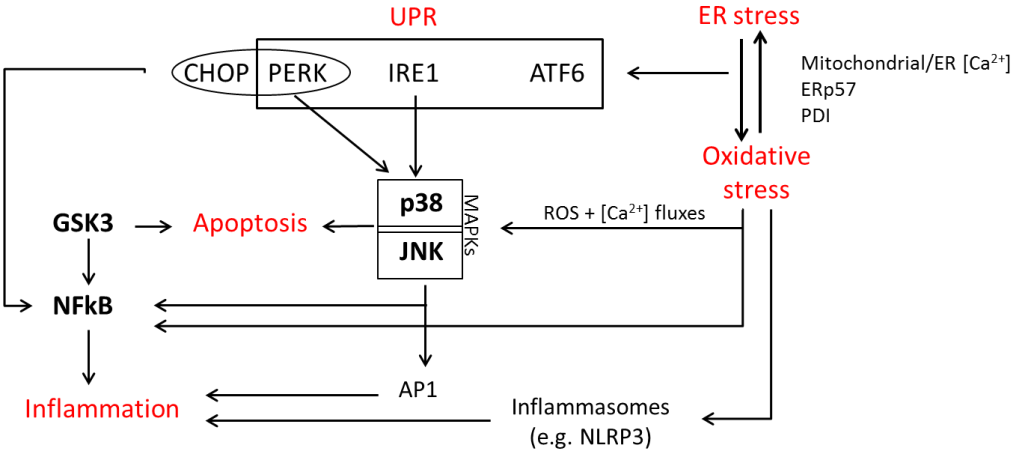

Figure 3. Schematic representation of the interacting pathways associated with oxidative and ER stress as well as UPR activation. Prolonged cellular stress causes sustained activation of GSK3, NFkB and the p38 and JNK branches of MAPK signaling pathways, therefore leading to inflammatory processes and apoptotic cell death. Activating interactions between pathways or factors are indicated with black arrows.
AP1: activator protein1; ATF6: activating transcription factor 6; CHOP: C/EBP-homologous protein; ERp57: redox chaperone ER resident protein 57; GSK3: glycogen synthase kinase 3; IRE1: inositol requiring kinase 1; JNK: c-Jun N-terminal kinase; NFkB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-like receptor containing pyrin domain 3; PDI: protein disulphide isomerase; PERK: PRK-like ER kinase.

(2) NFkB

NFkB is a key transcriptional regulator playing a central role in the onset of inflammation. Activation and subsequent translocation to the nucleus of NFkB is initiated by signal-induced phosphorylation of IkB, which is degraded immediately after activation of its substrate. IkB phosphorylation and subsequent NFkB activation following ER stress is due to the interaction of multiple converging factors including OS exacerbation, changes in intracellular Ca^{2+} fluxes and UPR activation. UPR alone can activate this pathway through the PERK and IRE1 branches [81]. The PERK-eIF2α-mediated attenuation of translation shifts the IkB-NFkB ratio towards the latter thereby increasing its availability in the nucleus. In parallel, the IRE1α-TRAF2 complex further promotes IkB degradation and NFkB-dependent transcription, through the activation of JNK pathway. Finally, activated JNK phosphorylates transcription factor activator protein 1 (AP1) which translocates to the nucleus [98] and together with NFkB contribute to pro-inflammatory gene expression.

Recent reports show that in parallel to NFkB pathway, OS and ER stress lead to activation of inflammatory processes through other systems namely inflammasomes. Inflammasomes are multiprotein complexes localized within the cytoplasm of the cell and are involved in the maturation

of proinflammatory cytokines, responsible for triggering a highly inflammatory form of cell death. Inflammasome function is modulated also by other phenomena such as potassium efflux, lysosome function, intracellular Ca^{2+}, ubiquitination and altered microRNAs balance. Up to date, the best known and most characterized inflammasome is the NOD-like receptor containing pyrin domain 3 (NLRP3), now emerging as a critical molecular mediator for degenerative diseases [99].

(3) GSK3

GSK3 is active in several central intracellular signaling pathways, including cellular proliferation, migration, inflammation and immune responses, glucose regulation, and apoptosis and is mediated by two protein isoforms: GSK3α and GSK3β. Both isoforms can be phosphorylated and the specific phosphorylation pattern affects kinase activity and activation of downstream targets. In fact, phosphorylation at Tyr-216 in GSK3β or Tyr-279 in GSK3α enhances the enzymatic activity of GSK3, while phosphorylation of Ser-9 in GSK3β or Ser-21 in GSK3α significantly decreases the availability of its active site [100].

In the context of neurodegeneration, the association between UPR and GSK3 has been studied in Alzheimer's disease (AD), in which the existence of a vicious cycle between UPR, GSK3 activation and tau pathology has been demonstrated by Scheper's group [101]. In particular, they showed that UPR activation increases the activity of the major tau kinase GSK3 *in vitro*, through the removal of inactive phosphorylated GSK3 Ser (21/9) via the autophagy/lysosomal pathway.

In vitro studies by Meares and collaborators demonstrated that inhibition of GSK3 pathway counteracted ATF4 and ATF6-triggered apoptosis, mainly by interfering with the expression and activation of CHOP [102], however not much information is available on other neurodegenerative disorders, such as PD and ALS. Considering the relevance of GSK3 in the regulation of metabolism, inflammation and cell viability, the UPR-GSK3 connection should be addressed in future studies.

(4) Autophagy, lysosomes and transcription factor EB pathway

The association between UPR and autophagy is very interesting: several reports show that autophagy represents a very intriguing system for controlling OS and cell viability and the outcome depends on the stimuli that trigger ER stress, the cell type, and the metabolic and (physio)pathologic context in which autophagy is activated [103,104].

Together with ERAD and other systems involved in macromolecules degradation, ER stress activates autophagy which is supposed to play a compensatory role and provide relief from misfolded protein burden. According to Scheper's group, autophagy is the preferential system triggered for protein degradation after ER stress in AD pathology [105]. Although in neurodegenerative diseases other than AD the cross-talk between ER stress, OS and autophagy is more complex and still largely unexplored [106,107], a recent review has addressed this topic [108].

Interestingly, growing evidence is supporting the role of transcription factor EB (TFEB) in the regulation of autophagy as well as lysosomal associated proteins (hydrolases, membrane proteins, proteins for lysosomal biogenesis) in pathologic conditions such as lysosomal storage disorders (LSD) and neurodegenerative disorders [93,109].

Again, not much is known about the association and possible overlap between ER stress-activated responses and TFEB. Ballabio's groups performed a study combining different genomic approaches to

identify the clusters of genes under TFEB control [110]. They highlighted a wide and variegated network including lysosome-related and autophagic genes, as well as other markers associated with signaling pathways (i.e. MAPK), metabolism and all cellular organelles, including ER. Considering the wide range of genes controlled by TFEB and the pivotal role that they play in affecting the progression of neurodegenerative disorders, it will be relevant to further investigate the impact of TFEB modulation in neurodegeneration with the intent to identify novel targets for disease-modifying therapeutic strategies.

5. Molecular and chemical chaperones support proteostasis and modulate OS and ER stress: disease-modifying potential in neurodegeneration

Chaperones are proteins responsible for supporting protein folding and their characterization in the context of ageing and disease is attracting the interest of both academic and pharmaceutical organizations for the impact that its modulation might have in the clinical field [111].

Studies carried out on diseases such as LSD and diabetes type 2, show the importance of using chaperone molecules or chaperone modulators to support proteostasis and therefore alleviate OS and ER stress and protect cells from undergoing apoptosis [112-115]. Several studies suggest a link between LSD and neurodegenerative disorders in terms of pathogenic mechanisms [116]. Therefore the assessment of the therapeutic potential of molecular chaperones in LSD might provide meaningful insights on the use of these same molecules in neurodegenerative diseases [117].

Endogenous chaperones are matter of investigation in neurodegeneration. For instance, DJ-1 protein, encoded by PD-associated gene *PARK7*, affect cell susceptibility to OS as well as ER stress and other death-inducing stimuli [118,119]. It plays a role as a redox-sensitive molecular chaperone responsible for modulating protein aggregation in different neuropathological conditions [120,121], further stressing the neuroprotective function of this protein across neurodegenerative disorders.

Also, the small secretory chaperone or proSAAS, widely expressed in neuronal cells, is associated with aggregated proteinacious deposits in the brains of patients with various neurodegenerative diseases, including PD. *In vitro* assays demonstrated that proSAAS inhibits α-syn fibrillation and exerts neuroprotective effects against α-syn-induced toxicity in primary cell cultures of dopaminergic neurons [122], thereby supporting a role for proSAAS as a therapeutic target in PD.

Another example is represented by heat shock proteins (HSPBs), a family of molecular chaperones. HSPBs have been indicated as protective because of their capacity of preventing unfolded proteins aggregation or, alternatively, counteracting OS and apoptotic phenomena [9,123]. In PD, some HSPBs such as Hsp70, Hsp90, Hsp104 and co-chaperones can prevent α-syn misfolding, oligomerization and aggregation *in vitro* and in animal models [124-126]. Furthermore, expression of some endogenous chaperones, including HSPBs, appears to be lower in dopaminergic neurons, possibly contributing to the peculiar susceptibility of these cells to α-syn aggregation and eventually death [127]. Similarly, in ALS it has been suggested that higher expression of HSPBs in muscle cells rather than motor neurons might explain why muscle cells are more capable of handling mutant SOD1 accumulation and are less vulnerable than motor neurons [128].

Chemical chaperones and chaperone modulators are also under extensive investigation in neurodegenerative diseases [68,129]. Among the best known are taurodeoxycholic acid (TUDCA), 4-phenylbutyrate (4-PBA), celastrol, ambroxol and isofagomine. These and other examples are reported in Table 2 [93,130-138].

Table 2. list of chemical chaperones or chaperone modulators showing neuroprotective potential

Compound and characterization	Mechanism of action	Disease	Reference
Ambroxol chemical chaperone	Increases *GBA*-encoded protein folding, activates TFEB and reduces OS in fibroblast primary cultures	PD and Gaucher's disease	PMID: 24574503
Arimoclomol hydroxylamine derivative	Induces and support the heat shock protein response under cellular stress conditions in different models of ALS (currently under Phase II clinical study for ALS)	ALS	Reviewed in PMID: 23978556
Celastrol	Increases glucocerebrosidase activity, by promoting heat shock protein and promoting ERAD	PD and Gaucher's disease	PMID: 24351928
Natural triterpene	Prevents rotenone-induced neurodegeneration by protecting mitochondrial integrity in SH-SY5Y	PD	PMID: 24214023
Docosahexaenoic acid (DHA) Omega-3 fatty acid IP3 receptors inhibitor	Reduces neuronal death and improves motor symptoms in a MPTP-induced rodent model of PD	PD	PMID: 21736911
Genistein phytoestrogen	Ameliorates motor deficit and protects nigral dopaminergic neurons in the 6-OHDA rodent model of PD	PD	PMID: 18693302
Guanabenz α2 selective adrenergic agonist (anti-hypertensive)	Modulates ER stress by reducing activation of UPR mediators and downstream activation of apoptotic factors in a mouse model of ALS (SOD1 G93A)	ALS	PMID: 24699224 PMID: 25134731
Isofagomine chemical chaperone	Abolishes microglial inflammatory response, reduces α-syn immunoreactivity in nigral dopaminergic neurons of a mouse model of PD (Thy1-aSyn)	PD	PMID: 25037721
4-phenylbutyrate (4-PBA) chemical chaperone	Reduces neuronal death and rotenone-induced α-syn accumulation Improves motor deficits and reduces dopaminergic neuronal loss in the SNc of a PD mouse model over-expressing mutant α-syn (A30P+A53T)	PD PD	PMID: 17459145 PMID: 19345133
Salubrinal	Protects against rotenone-induced toxicity in a cellular model of PD (SH-SY5Y) via parkin-mediated mechanisms	PD	PMID: 24418467
eIF2α phosphatase inhibitor	Attenuates motoneuron disease in a mouse model of of ALS by modulating ER stress	ALS	PMID: 19330001
Trehalose	Protects dopaminergic neurons, striatal terminals as well as brain blood vessels and improves motor deficit against MPTP-induced toxicity in mice	PD	PMID: 25064079
Ursodeoxycholic acid (TUDCA) amphilic bile acid	Rescues mitochondrial function in fibroblasts from PD patients carrying *PARK2* mutations Reduces UPR activation and locomotor impairment in a mouse model of adrenoleukodystrophy (ALD)	PD ALD	PMID: 24000005 PMID: 28004277

Interestingly, nanotechnologies are also interested in the development of structures and/or particles for chemical chaperone delivery. For instance, nanotube hydrogels have been engineered to support folding of various target proteins of different molecular weights, charges, and conformations. This is mainly based on the possibility to adapt the diameters of the nanotube channels, to functionalize their surfaces, enabling to fine-tune the biocompatibility [139].

Furthermore, nanotechnologies are focusing on the design of nanoparticles that promote protein clearance by sustaining the autophagy-lysosome system, with critically interesting applications in the biomedical field (e.g. drug delivery) [140]. Some of these particles have already been tested for their capability of counteracting apoptosis and OS or interfering with protein aggregation and with the formation of toxic oligomers in neurodegenerative conditions [141-143].

6. Conclusions

Neurodegenerative disorders such as PD and ALS share common pathogenic mechanisms including altered proteostasis and OS. The role of UPR, however, is still a matter of debate due to the complexity of responses that are generated at the ER level depending on the phase of disease progression and neuronal damage. Persistent OS and ER stress sustain each other, eventually activating detrimental factors and signaling pathways leading to inflammation and apoptotic death.

Molecular chaperones support protein folding, modulate UPR and promote mitochondrial and lysosomal function and are currently under investigation in several pathologic conditions, including neurodegeneration, for their ability of supporting cell viability.

Further investigation on the use of endogenous and chemical chaperones as well as nano-engineered tools with chaperoning function in PD and ALS may help to elucidate novel targets and therapeutic strategies for disease-modifying drugs in this area of high unmet medical need.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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