ER stress and Parkinson's disease: Pathological inputs that converge into the secretory pathway

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A B S T R A C T

The major clinical feature of Parkinson's disease (PD) is impairment in motor control as a result of extensive dopaminergic neuron loss in the substantia nigra pars compacta. The central pathological hallmark of PD is the formation of neuronal cytoplasmic inclusions of insoluble proteins called Lewy bodies, of which fibrillary aggregates of misfolded αSynuclein are the major components. Despite intense research on the pathogenic mechanism that trigger neuronal loss and disease progression, the neurogenesis of PD remains unknown. However, studies on genetics of PD have identified specific genes and proteins linked to this disease. Genetic mutations linked with different forms of familial PD have unveiled a closer relationship between pathology and impairments at different points in the secretory pathway. Accumulation of misfolded/unfolded proteins in the endoplasmic reticulum and disruptions in protein clearance mechanisms result in activation of an adaptive stress pathway known as the unfolded protein response (UPR). UPR signaling is mediated by three stress sensors that induce independent and convergent signaling branches that help to maintain homeostasis, or eventually trigger cell death under chronic stress conditions. Signs of ER stress are observed in post-mortem tissue from sporadic human PD cases and in most animal models of the disease, implicating all three branches of this cellular response. However, the exact contribution of the UPR in the progression of PD or in dopaminergic neuron survival is not yet well understood. A large number of studies reveal a clear activation of the UPR in toxicological models resembling sporadic PD, where ATF6, XBP1 and CHOP have a functional role in controlling dopaminergic neuron survival in neurotoxin-based models of PD in vivo. Also pharmacological and gene therapy approaches aimed to target different points of this pathway have revealed an important functional role in PD pathogenesis.

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Abbreviations: PD, Parkinson’s disease; SNpc, substantia nigra pars compacta; LB, Lewy bodies; αSyn, α-synuclein; ER, endoplasmic reticulum; ERAD, ER-Associated Degradation; PINK1, PTEN-induced putative kinase 1; ATP1A2, lysosomal P-type transport ATPase; LRKK2, leucine-rich repeat kinase 2; VPS35, vacuolar protein sorting-35 protein; UCHL-1, ubiquitin carboxy-terminal hydrolase L1; GCase, β-glucocerebrosidase; DAT, dopamine transporter; SNARE, soluble NSF attachment protein receptor; TFEB, transcription factor EB; CHIP, C-terminus of Hsp70-interacting protein; Pael-R, parkin-associated endothelin receptor-like receptor; UPR, unfolded protein response; IRE1α, RNA-activated protein inositol requiring kinase 1; BiP, Glucose regulated protein 78 (Grp78); XBP1β, transcription factor X-Box binding protein 1; eIF2α, eukaryotic initiation factor 2; GADD34, growth arrest and DNA damage-inducible protein 34; CHOP, C/EBP homologous protein; MPP+, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; AAV, adeno-associated viral vectors

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1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease and affects about 1% of the elderly population. A known risk factor for PD is age, suggesting that its prevalence is likely to increase in the next several years. PD is a progressive neurodegenerative disease that impairs movement control, and is often accompanied by dementia. PD is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and by the presence of intraneuronal inclusions, termed Lewy bodies (LB), where fibrillar aggregates of α-synuclein (αSyn) constitute a major component (Spillantini et al., 1997).

As in all neurodegenerative diseases, PD represent a major challenge in terms of a large and rapidly increasing population that is afflicted and the lack of effective treatments. The ultimate objective for a disease-modifying therapy is to slow down or even stop disease progression. To accomplish this goal, research focused on genetics and pathophysiology of the disease is fundamental to understand the process of dysfunction and degeneration.

A major focus of study in the field is the understanding of the mechanisms involved in the selective neuronal vulnerability of dopaminergic neurons in PD. Recent accumulating evidence supports the concept that disruptions in the secretory pathway function is an important contributor to the pathogenic processes, ultimately leading to aggregated protein accumulation and dopaminergic neuron loss in PD.

2. Secretory pathway dysfunctions and PD

Genetic mutations linked to different forms of familial PD have unveiled a closer relationship between pathology and different points in the secretory pathway (Fig. 1). The secretory pathway is not only composed of the endoplasmic reticulum (ER) and Golgi compartments but is formed by the entire biosynthetic–secretory and endocytic pathways. In these pathways, proteins and other cellular components are transported by a complex network of vesicular compartments that fission and fuse from the ER to Golgi to the cell exterior and back to early endosomes and lysosomes via recycling pathways, and even back to the ER. Recently, the generation of neuronal cultures from induced pluripotent stem cells derived from PD patients, indicated that ER stress leads to accumulation of ER-Associated Degradation (ERAD) substrates and that ER stress is a salient molecular signature of the disease (Chung et al., 2013).

Causes of PD are mostly sporadic with no or not yet identified genetic cause(s), and it is estimated that only 5–10% of patients exhibit monogenic forms of the disease (Lesage and Brice, 2009). Some of the identified genes involved in autosomal recessive PD are the ones that codified for the ubiquitin E3 ligase, Parkin, PTEN-induced putative kinase 1, (PINK1), protein deglycase DJ-1, and the lysosomal P-type transport ATPase (ATP13A2). Genes involved in autosomal dominant PD are SNCA locus that encode αSyn protein, leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting-35 (VPS35), and ubiquitin carboxy-terminal hydrolase L1 (UCHL-1) (Klein and Westenberger, 2012). In addition, genome-wide association studies found that LRRK2, αSyn, β-glucocerebrosidase (GCase) and dopamine transporter (DAT), are common risk factors for sporadic PD (Mullin and Schapira, 2015).

Mutations within αSyn as well as duplication and triplication of the SNCA locus, result in an acceleration of pathogenic aggregation of this protein and neurodegeneration (Conway et al., 2000; Chartier-Harlin et al., 2004; Choi et al., 2004; Kruger et al., 1998; Polymeropoulos et al., 1997; Zarranz et al., 2004). αSyn is predominately a presynaptic terminal protein and despite its relevant role in the pathophysiology of PD, the physiological function and the molecular pathways mediating αSyn neurotoxicity remains unsolved. It has been described that the physiological function of the protein would be chaperone soluble NSF attachment protein receptor (SNARE) complex assembly at the synapse (reviewed in Burre (2015)). In contrast, its pathological function would be related to its misfolded conformation leading to neurotoxic aggregates that are characteristic of the disease. Homozygous SNCA knockout mice do not display any PD phenotype, although there are some reports of mild impairment in vesicle trafficking and dopamine release (Abeliovich et al., 2000; Cabin et al., 2002; Chandra et al., 2004).

Cellular studies show a functional relationship between αSyn and Rab1 in yeast, and Rab3a in mammalian cells, where impairment of vesicle exit from the ER triggers the accumulation of immature proteins from this compartment (Cooper et al., 2006; Thayanidhi et al., 2010). Overexpression of Rab1 rescues dopaminergic neuron loss induced by αSyn overexpression. Additionally, more recent studies in the field indicate that overexpression of mutant αSyn triggers chronic ER stress, inducing cell death, possibly due to a block in ER to Golgi vesicular trafficking of ATP6 (Credle et al., 2015).

Under physiological conditions, αSyn is usually degraded by the autophagy–lysosome system including chaperon-mediated autophagy and the ubiquitin–proteasome system (reviewed in da Fonseca et al. (2015)). In pathological conditions, αSyn can impair all these degradation pathways, and furthermore, disturbances in the autophagy-lysosomal system can contribute to its toxicity and accumulation in the cell, triggering ER stress (Chu et al., 2009; Decressac and Bjorklund, 2013; Winslow et al., 2010). Additional evidence that autophagy increase clearance of αSyn and LB came from in vivo studies, where treatments with the autophagy inducer trehalose reduce aggregate αSyn levels in mice and rats (He et al., 2015; Tanji et al., 2015), and even improve motor performance in a rat model of PD (He et al., 2015).

In this regard, it has recently been shown that αSyn-mediated toxicity in nigral dopaminergic neurons is accompanied by the cytosolic retention of transcription factor EB (TFEB), a major transcriptional factor of the autophagy-lysosomal pathway, possibly by a direct protein:protein interaction (Decressac et al., 2013). Moreover, in vivo manipulation of TFEB levels can modify αSyn mediated toxicity (Decressac et al., 2013). In cellular models, it has been described that TFEB can translocate to the nucleus in response to ER stress (Martina et al., 2016).

One of the recently described PD genes encodes for the vacuolar protein sorting-35 (VPS35) protein of the retromer complex that plays an essential role in endosome-to-Golgi retrieval of membrane proteins. A D620N mutation in the VPS35 gene has been identified in patients with autosomal dominant PD (Vilarino-Guell et al., 2011). Dysfunction of this gene in Drosophila models increased αSyn accumulation in lysosomes and impaired locomotion (Miura et al., 2014). VPS35-deficient mice exhibited PD-relevant deficits including accumulation of αSyn in nigral dopaminergic neurons,
loss of dopamine transmitters and dopaminergic neurons in SNpc and striatum, along with impairment of locomotor behavior. Importantly, VPS35-deficient dopamine neurons or dopamine neurons expressing the PD-linked VPS35 mutant (D620N) have impaired endosome-to-Golgi retrieval of lysosome-associated membrane glycoprotein 2a (Lamp2a), with acceleration of Lamp2a degradation (Tang et al., 2015). Expression of Lamp2a in VPS35-deficient dopamine neurons reduced αSyn toxicity, implicating Lamp2a, a receptor of chaperone-mediated autophagy, to be critical for αSyn degradation (Tang et al., 2015).
Although it appears that in pathological conditions αSyn protein is less efficiently cleared (Fig. 1), leading to its accumulation and LB formation, the exact mechanism by which αSyn triggers neurodegeneration remains unclear. ER stress is a downstream pathway which converges the described pathological dysfunctions among the secretory pathway and, thus, its manipulation in disease context may unveil potential therapeutic value.

Another example of the interrelation between PD pathology and dysfunctions in the secretory pathway involving ER stress is the recently described association with Gaucher disease, a common lysosomal storage disorder. Gaucher disease, resulting from mutations in the gene GBA1 encoding the lysosomal hydrolase β-glucocerebrosidase (GCase), leads to lysosomal dysfunction, stabilizing toxic oligomeric forms of αSyn and blocked export of newly synthesized GCase from the ER to late endocytic compartments (reviewed in Blanz and Saftig (2016)). A recent study found evidence of increased GCase retention within the ER leading to an increase in reactive oxygen species production and cellular stress (Mazzulli et al., 2011). Encouragingly, pharmacological treatment in cell culture models with the pH-dependent GCase inhibitor, ambroxol, appears to reduce αSyn levels and restore GCase activity possibly by facilitating trafficking of GCase through the ER (reviewed in Maor et al. (2013)).

Lysosomes are critical for protein and lipid homeostasis, and recent research revealed that dysfunction of this organelle contributes to the development of neurodegenerative diseases including PD. Mutations in the lysosomal protein ATP13A2 cause a rare form of early onset parkinsonism, leading to its retention at the ER, triggering the induction of chronic ER stress and cell death (Park et al., 2011). Loss of ATP13A2 in vivo causes age-related motor dysfunction and endo-lysosomal dysfunction, defects that are independent of αSyn expression (Kett et al., 2015). Mutations in LRRK2 are the most frequent genetic defect identified in PD patients (Kumari and Tan, 2009). LRRK2 partially localizes to the ER in dopaminergic neurons of PD patients (Vitte et al., 2010). Studies in Caenorhabditis elegans demonstrated that expression of wild-type LRRK2 protects dopaminergic neurons against the PD-inducing neurotoxin 6-hydroxydopamine (6-OHDA) or human αSyn-induced neurotoxicity (Yuan et al., 2011). C. elegans lacking the LRRK2 homologue develops spontaneous neurodegeneration and hyper-susceptibility to experimental stress (Samann et al., 2009). Although the function of LRRK2 remains a matter of constant debate, its seems to converge on ER export and secretory trafficking (reviewed in Wang and Hay (2015)). LRRK2 is required for the ER exit site assembly and efficient ER cargo exit (Cho et al., 2014). This scaffold protein has been also associated with trans-Golgi-network turnover, where over-expression of wild-type or disease-associated mutations led to trans-Golgi-network marker ablation possibly leading to accumulation of secretory cargo (Beilina et al., 2014).

LRRK2 and αSyn are substrates for ERAD-related E3, C-terminus of Hsp70-interacting protein (CHIP), and Parkin, suggesting that disturbances in the ERAD system are relevant to the onset of PD (Ding and Goldberg, 2009; Imai et al., 2000; Ko et al., 2009; Shimura et al., 2000). In contrast to αSyn and LRRK2, a few and unconnected studies suggest that other PD-linked genes such as UCHL-1 and DJ-1 can alter ERAD function or enhance the susceptibility of cells to ER stress (reviewed in Mercado et al. (2013)). Expression of Parkin-associated endothelin receptor-like receptor (Pael-R), a substrate of the ubiquitin E3 ligase Parkin, induces ER stress and neurodegeneration in the SNpc of mice (Kitao et al., 2007; Kubota et al., 2006). The effects of Pael-R on ER stress are enhanced by Parkin deficiency (Kitao et al., 2007). Another identified ubiquitin E3 ligase, HRD1, interacts with unfolded Pael-R and colocalizes in the ER of a cellular model of PD suppressing Pael-R-induced cell death (reviewed in Omura et al. (2013)).

A series of conditions including accumulation of misfolded/unfolded proteins at the ER, mutations in proteins that traffic through the secretory pathway, disruptions in protein clearance mechanisms (autophagy-lysosomal pathway and ERAD) and altered calcium homeostasis, among others, can altered ER homeostasis activating the UPR, a complex signaling transduction pathway that mediates cellular adaptation to restore ER homeostasis (reviewed in Vidal and Hetz (2012)).

3. The UPR and PD

The UPR is a signaling network mediated by the activation of three main stress sensors located at the ER membrane, including inositol requiring kinase 1α (IRE1α), activating transcription factor 6 (ATF6), and protein kinase RNA-like ER kinase (PERK) (Fig. 1). These UPR transducers control the expression of a variety of genes involved in almost every aspect of the secretory pathway, resulting in a reduction in load of misfolded proteins at the ER. Activation of the UPR improves the efficiency of protein folding and quality control mechanisms, in addition to enhance ER and Golgi biosynthesis, protein secretion and the clearance of abnormally folded proteins through the autophagy and ERAD pathways. However, under chronic ER stress UPR sensors shifts their signaling toward induction of cell death by apoptosis through different complementary mechanisms, eliminating irreversibly damaged cells (Urre et al., 2013).

The ER chaperone Glucose regulated protein 78 (Grp78/BiP) is a key regulator of the UPR, since its binding to the three stress sensors maintains the UPR on an inactive state. Upon accumulation of misfolded proteins within the ER, BiP dissociates from UPR sensors inducing their activation. IRE1α is a serine-threonine kinase and endoribonuclease that, upon activation, initiates the processing of the mRNA encoding the transcription factor X-Box binding protein-1 (XBP1) (Ron and Walter, 2007). This event excises a 26-nucleotide intron, shifting the coding reading frame of the mRNA that results in the expression of a more stable and active transcription factor, termed XBP1s. XBP1s regulates the expression of a subset of UPR-target genes related to folding, ER/Golgi biogenesis and ERAD (Hetz et al., 2011). ATF6 encodes a transcription factor in its cytosolic region. Upon dissociation from BiP, ATF6 traffics to the Golgi and undergoes subsequent proteolytic processing to release ATF6f, an active transcriptional factor (Ron and Walter, 2007). ATF6f can induce independently or synergistically with XBP1s a cluster of genes involved in protein quality control among other targets (Shoulders et al., 2013).

PERK is an ER-located kinase that upon activation phosphorylates the eukaryotic initiation factor 2α (eIF2α). This event results in a general attenuation of protein translation, contributing to decrease the overload of proteins at the ER (Harding et al., 1999), eIF2α phosphorylation in turn leads to the specific translation of activating transcription factor 4 (ATF4), which upregulates many important genes functioning in redox control, amino acid metabolism and protein folding (Harding et al., 2003). Under chronic stress, ATF4 regulates the expression of pro-apoptotic genes such as the C/EBP-homologous protein (CHOP), the growth arrest and DNA damage-inducible protein 34 (GADD34) and components of the BCL-2 family (Tabas and Ron, 2011). GADD34 participates on a feedback loop to reestablish protein translation levels by inducing the dephosphorylation of eIF2α. This regulatory step is mediated by the formation of a complex between GADD34 and protein phosphatase 1C (PP1C) (Novoa et al., 2001). Under resting conditions the complex is formed by the constitutively expressed phosphatase CReP and PP1C, mediating eIF2α dephosphorylation in unstrressed cells (Joussie et al., 2003).

Usually activation of the UPR is a transient event, allowing
normal transcriptional profiling to restore, and normal protein translation to restart. However, under chronic ER stress the UPR triggers cell death by apoptosis, to eliminating damaged cells. The mechanisms leading to ER stress in PD and the actual impact of the UPR on the degeneration cascade in the disease are just starting to be uncovered. Next, we summarize most novel insights revealing a functional link between different UPR branches and the pathophysiology of PD. For a more global review of the role of UPR in PD pathology see Mercado et al. (2013).

3.1. The ATF6 branch

Three knockout animals for UPR components have been used in PD studies. In ATF6 deficient animals, the accumulation of ubiquitin-positive inclusions and the loss of dopaminergic neurons induced by the PD-triggering neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is enhanced (Egawa et al., 2011), suggesting that activation of the UPR has an important adaptive function to maintain protein homeostasis in this model. Although ATF6 is not essential for development and survival of dopaminergic neurons in mice, this stress sensor controls the levels of BiP and ERAD components under resting conditions in dopaminergic neurons (Egawa et al., 2011).

A recent study in cellular PD models determined that under ER stress, αSyn inhibits ATF6 possessing, both directly through physical protein:protein interaction of αSyn with ATF6 and indirectly, through restricted incorporation of ATF6 in COPII vesicle, diminishing its ER-Golgi transport (Credle et al., 2015). Inhibition of ATF6 incorporation into COPII vesicles was also mimicked by a αSyn mutant, A53T, where lower levels of ATF6 were seen in COPII in the presence of this mutant. In addition to these effects, it was found that αSyn altered the biophysical properties of COPII vesicles (Credle et al., 2015). Impairment of ATF6 trafficking to the Golgi resulted in the misprocessing of ATF6, with reduced levels of ATF6 seen in nucleus of cells. Since ATF6 is the neuroprotective branch of the UPR, reduction in ATF6 is likely to trigger apoptosis, with activation of the pro-apoptotic IRE1α and PERK branches of the UPR. This also leads to an impaired up-regulation of ERAD genes, which sensitizes cells to apoptosis, thereby disrupting UPR signaling (Credle et al., 2015).

3.2. The IRE1α/XBP1 branch

A set of in vivo studies showed the role of the UPR transcription factor XBP1s in controlling the survival of dopaminergic neurons (Valdes et al., 2014). Preconditioning of the ER has been used as neuroprotective strategy in animal models of PD (Mollerieu et al., 2014, 2016). The developmental ablation of XBP1 preconditions dopaminergic neurons, rendering them resistant to the PD-triggering neurotoxin, 6-OHDA. This preconditioned effect is accompanied by the up-regulation of UPR markers in the SNpc of animals resulting in the misprocessing of ATF6, with reduced levels of ATF6 being seen in nucleus of cells. Since ATF6 is the neuroprotective branch of the UPR, reduction in ATF6 is likely to trigger apoptosis, with activation of the pro-apoptotic IRE1α and PERK branches of the UPR. The XBP1s transgene also protects dopaminergic neurons against MPTP-induced degeneration in mice, when is delivered into the striatum using recombinant adeno-viral vectors (Sado et al., 2009).

XBP1 over-expression is also neuroprotective in C. elegans models of αSyn-induced dopaminergic neuron degeneration, whereas neuron-specific RNAi knockdown of XBP1 exacerbates neurodegeneration (Ray et al., 2014). The unconventional splicing of XBP1 is catalyzed by an endoribonuclease IRE1α and a recently described RNA ligase, RTCB-1 (Kosmacewski et al., 2014). This ligase, which also confers protection to dopaminergic neurons against αSyn overexpression in C. elegans, uncovered a functional relationship between XBP1 and its ligase in the regulation of neuroprotection against proteostatic stress in these neurons (Ray et al., 2014).

It has been observed that XBP1 is not only protective when delivered by viral transduction into dopaminergic neurons, but also when it is delivered in neural stem cells transfected with this transcription factor (Lihui et al., 2012). In these cells XBP1 transfection results in increased survival and improved behavior in a rotenone-induced rat model of PD (Lihui et al., 2012).

With this background in mind, in the case of XBP1s, it becomes very important to test its protective capacity and possible therapeutic function in pre-clinical genetic models of the disease that better recapitulate the human pathology than toxicological models.

Among other functions, XBP1s and ATF6f mediate the transcription of BiP. The over-expression of this chaperone also protects dopaminergic neurons and increases motor performance in a rat model of PD, induced by the direct injection of αAβs encoding for human αSyn into the SNpc (Gorbatyuk et al., 2012). This protection is accompanied by a global down-regulation of ER stress response (Gorbatyuk et al., 2012). It has been also demonstrated that age-related decline in BiP expression as well as siRNA-mediated down-regulation, increases dopaminergic neuron vulnerability to αSyn in the same PD model (Salganik et al., 2015).

Thus, increasing evidence indicates that the local modulation of the UPR in the nigro-striatal circuit may have important therapeutic potential in PD.

3.3. The perk/ATF4 branch

The UPR is a double-edged sword, cytotoxic when activated to a moderate extent, but signaling cell death upon severe and sustained stress. It was found that IRE1α and ATF6 activities are attenuated by persistent ER stress. However, signaling from PERK, which causes translational inhibition and expression of CHOP was maintained, driving the cell towards apoptosis (Lin et al., 2007).

In the case of PD, markers of the activation of PERK/elf2α branch have been found in PD post-mortem tissue, where nigral dopaminergic neurons displaying αSyn inclusion were also positive for phosphorylated PERK and elf2α (Hoozemans et al., 2007). Additional evidence implicating this pathway come from another mouse model, in which the deletion of CHOP protects dopaminergic neurons against the parkinsonian neurotoxins 6-OHDA and MPTP in different experimental settings (Silva et al., 2005). The pharmacological modulation of this branch is currently employed in different disease contexts. Salubrinal is a small compound that enhances elf2α phosphorylation by inhibiting its phosphatases (Boye et al., 2005). Salubrinal treatment delays disease onset and attenuates motor deficits of a rat viral-based model of PD.
consistent with αSyn overexpression (Colla et al., 2012). However, salubral treatment did not protect dopaminergic neurons from degeneration (Colla et al., 2012). Similar effects were observed in mutant αSyn transgenic mice associated with increased expression of UPR target genes in the brain including BiP. Unexpectedly, salubral administration reduced the accumulation of αSyn in ER-enriched fractions (Colla et al., 2012).

In this regard, new exciting findings implicate PERK/ATF4 branch of the UPR as a mediator in the neurodegeneration observed in several protein misfolded diseases suggesting that general protein translation shut down is the mechanism underlying neuronal dysfunction and degeneration (Halliday et al., 2014). Moreover, there are now several tools available to study the PERK/ATF4 branch of the UPR, through pharmacological or genetic manipulation (Hetz and Mollereau, 2014). In this scenario, it would be interesting to test if general protein translation shut down is the mechanism underlying dopaminergic neuron degeneration, and to test the therapeutic potential of new small molecules targeting the PERK/ATF4 branch in different PD models.

4. Concluding remarks

Taken together, all these findings suggest that a common feature in sporadic and different genetic forms of PD are dysfunction at different points of the secretory pathway that converge in the occurrence of ER stress, where the available tools to manipulate this stress response pathway, by genetic or pharmacological means, offer a unique target for therapeutic intervention. However, most of the studies relating ER stress to PD are correlative or performed in vitro. Thus, in vivo manipulation is required to define the impact of targeting specific components of the pathway in PD and elucidating their therapeutic potential. An important point to unveil novel therapeutic targets is to delineate the mediators in the cross-talk between dysfunction of the secretory pathway, and the duration and intensity of the ER stress, which contribute to a large degree to the cell decision between survival or death.

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