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Misfolded proteins, endoplasmic reticulum stress and neurodegeneration

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Abstract

The accumulation of misfolded proteins (e.g. mutant or damaged proteins) triggers cellular stress responses that protect cells against the toxic buildup of such proteins. However, prolonged stress due to the buildup of these toxic proteins induces specific death pathways. Dissecting these pathways should be valuable in understanding the pathogenesis of, and ultimately in designing therapy for, neurodegenerative diseases that feature misfolded proteins.

Introduction

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and prion protein diseases all share a common feature: the accumulation and aggregation of misfolded proteins [1–3]. The presence of misfolded proteins elicits cellular responses that include an endoplasmic reticulum (ER) stress response that may protect cells against the toxic buildup of misfolded proteins [3–7]. Accumulation of these proteins in excessive amounts, however, overwhelms the 'cellular quality control' system and impairs the protective mechanisms designed to promote correct folding and degrade faulty proteins, ultimately leading to organelle dysfunction and cell death [1–10].

Since the degradation of cellular proteins in general is coupled, via the ubiquitin-mediated proteasomal degradation pathway, to ER dislocation of many ER substrates [3,9,10], any conditions that block ER retrotranslocation of proteins and/or proteasome function and degradation may also result in the accumulation of misfolded protein substrates within the ER. Thus, misfolded proteins trigger the ER stress response, whether the misfolded proteins build up within, or outside, the ER (e.g. in the nucleus or cytosol) and transmit toxic responses across cellular compartments. Misfolded proteins may be deposited as microscopically visible inclusion bodies or plaques within cells or in extracellular spaces, and have a high propensity to interact with a wide range of cellular targets to elicit cellular toxicity [1]. Toxicity may arise due to one or more of a number of factors: inhibition of synaptic function; loss of synpases leading to disruption of neuronal functions; sequestration of critical cellular chaperones and vital transcription factors by misfolded proteins; interference with numerous signal-transduction pathways; alteration of calcium homeostasis; release of free radicals and consequent oxidative damage; dysfunction of the protein degradation pathway through the ubiquitinproteasome system; and/or induction of cell-death proteases leading to programmed cell death.

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This review highlights recent advances in understanding the complex regulation of ER stress and the unfolded protein response (UPR), and their relevance to apoptosis and neurodegenerative diseases that feature misfolded proteins.

Endoplasmic reticulum stress

The ER is a principal site for biosynthesis of proteins, steroids, cholesterol and other lipids. It also serves as a site of calcium storage and calcium signaling. The ER serves several important functions, including the post-translational modification, folding and assembly of newly synthesized secretory proteins, and its proper functioning is essential to cell survival. Nascent secretory and membrane proteins that are translocated into the ER lumen start to fold co-translationally. Post-translational modification, including proper folding, assembly of individual subunits and oligomerization, is necessary for optimal function. Each co-translational and post-translational step requires specific and sequential interaction with a distinct chaperone protein. These chaperone proteins perform diverse roles, including catalyzing isomerization reactions, maintaining proteins in a folding-competent state, preventing luminal protein transit through the secretory pathway, and regulating retro-translocation of misfolded proteins for degradation. Besides providing a unique oxidizing environment for protein folding, the ER also plays a critical role in discriminating between normal (native) and abnormal (mutant) proteins. As a membranous compartment associated with the critical functions mentioned above, the ER is extremely sensitive to changes that affect its structure, integrity and function. [6,8,11,12]. Thus, changes in calcium homeostasis leading to calcium depletion from the ER lumen, inhibitors of protein glycosylation, inhibitors of disulfide-bond formation, virus infection, hypoxia, ischemia and growth factor depletion can all disrupt protein synthesis, translation and folding, resulting in unfolded or misfolded proteins. The accumulation of unfolded and/or misfolded proteins causes an imbalance between the synthesis of new proteins and the ER's ability to process newly synthesized proteins, resulting in the failure of the ER to cope with the excess protein load, which is termed 'ER stress' [5,8,13–15]. Cells in turn activate an integrated intracellular signaling cascade — the 'unfolded protein response' — to avert ER stress.

The unfolded-protein response

In cells from all organisms, ER stress may elicit a set of cellular responses collectively referred to as the UPR [11,12,16,17] (Figure 1). UPR activation results in, first, a transient attenuation in the rate of protein synthesis, second, an upregulation of genes encoding chaperones and other proteins that prevent polypeptide aggregation and participate in polypeptide folding, and third, retro-translocation and degradation of ER-localized proteins. These cellular responses minimize the accumulation and aggregation of misfolded proteins by increasing the capacity of the ER machinery for folding and degradation [11,16,18] (Figure 1).

UPR and the molecules involved in the UPR signaling pathway were first described in the yeast *Saccharomyces cerevisiae*. In eukaryotes, the UPR is a is a coordinated, regulated response involving three sensor proteins: PERK (PKR-like ER kinase), IRE1 (inositol-requiring transmembrane kinase/endoribonuclease) and ATF6 (activating transcription factor 6) [14] (Figure 1). The presence of misfolded proteins and UPR activation triggers PERK oligomerization and autophosphorylation. Active PERK phosphorylates eukaryotic translation initiation factor 2α (eIF2α), rendering it inactive and blocking protein translation. Inactivation of eIF2α prevents the further influx of nascent proteins into the ER lumen, thus limiting the incoming protein load [19–22] (Figure 1).

The accumulation of misfolded proteins and UPR activation also lead to the translocation of ATF6 to the Golgi compartment, where it undergoes regulated intramembrane proteolysis (RIP) by proteases S1P and S2P, yielding a free cytosolic domain that, following nuclear translocation, triggers transcriptional upregulation of ER chaperone proteins like GRP78 and of bZIP transcription factors like CHOP/GADD153 [23,24•,25,26••, 27••,28–30]. The chaperone proteins facilitate and promote the productive folding of proteins and protein complexes, maintaining them in a folding-competent state and preventing their aggregation. UPR activation also induces homodimerization, autophosphorylation and activation of IRE1, an ER resident transmembrane serine/ threonine kinase receptor protein that also possesses an intrinsic endoribonuclease activity. Activated IRE1 cleaves a preformed substrate mRNA at two sites through its endoribonuclease action, resulting in the removal of a 26-nucleotide intron from a target mRNA [31–33]. The two ends of the cleaved mRNA are ligated together by tRNA ligase and the newly formed mRNA encodes a transcription factor X-box-binding protein (XBP-1). XBP-1 binds and activates the promoters of several ER-stress-inducible target genes that facilitate the retro-translocation and ER-associated degradation of misfolded proteins [26••,27••,34]. Thus, all of the above-mentioned specific signaling pathways that constitute the UPR operate to ensure that the protein folding capacity of the ER is not overwhelmed (Figure 1).

GRP78: the master regulator

The glucose-regulated proteins (GRPs) are Ca^{2+}-binding chaperone proteins with protective properties whose transcription is induced in response to several stimuli that disrupt ER structure and function [6,17]. One of the best-characterized glucose-regulated proteins is GRP78, a 78 kD protein also referred to as BiP. The induction of GRP78 is required to block ER stress signals, maintain ER function and integrity, ensure protein folding and protect cells from misfolded protein toxicity [6,17]. It has been well established that diverse misfolded proteins that accumulate in the cell trigger the same ‘quality control’ pathway, mainly by converging on GRP78, the ‘master molecule’. GRP78 binds to all three ER stress sensors (PERK, IRE1 and ATF6) through its peptide-binding domains, and keeps them in an inactive conformation [18,30,35,36] (Figure 2). The peptide-binding domain of GRP78 also serves as the binding region for misfolded proteins. When misfolded proteins accumulate in the cell, they bind to GRP78 and disrupt its interaction with these proximal stress sensors [11,16,18,36]. While free IRE1 and PERK homodimerize and undergo autophosphorylation and activation, ATF6 transits to the Golgi for proteolytic activation.

Although GRP78 exists as an ER lumen protein [6,17], several reports have suggested that GRP78 and its mutant forms may alternatively be expressed on the cell surface, exist as ER transmembrane proteins, or redistribute to the cytosol and nucleus [37–41,42•,43•]. Recent studies indicate that either a cytosolic pool of GRP78, or a subpopulation of GRP78 existing as an ER transmembrane protein, may associate with caspases-7 and -12 and prevent their activation and release [42•,43•]. These studies highlight the importance of GRP78 as an anti-apoptotic protein, and provide a link between ER stress, the unfolded protein response and the cell death program.

ER-stress-induced cell death

As stated earlier, prolonged ER stress and UPR activation completely overwhelm the cellular protective mechanisms, ultimately triggering cell death. Although there are several reports implicating various molecules as mediators of ER-stress-induced cell death, the pathway that links ER stress to programmed cell death is still relatively poorly understood. It has generally been assumed that the elimination of cells undergoing severe ER stress is desirable at the organismal level, and the upregulation of GRP78 in some malignant tumors

is compatible with (although not proof of) this notion [43•,44] In any case, prolonged ER stress is indeed coupled to specific independent death pathways, as well as triggering cross-talk between the intrinsic and extrinsic apoptotic pathways.

Studies from multiple laboratories have uncovered the roles of several ER-stress-induced cell death modulators and effectors through the use of biochemical, pharmacological and genetic tools. The ER-stress-induced cell death modulators include (but are not limited to) members of the Bcl-2 family (Bcl-2, Bcl-x_L, Bax, Bad, Bik, Noxa, and Bak) [45–47], p29Bap31 [48–50], c-Abl tyrosine kinase [51], and p53-dependent gene products like PUMA/Bbc3 and scotin [52,53]. Bcl-2 family members including Bcl-2, Bcl-x_L, Bax, Bad, Bik and Bak have been shown to be associated with the ER, suggesting the involvement of the Bcl-2 family proteins in ER calcium homeostasis and ER-stress-induced cell death [54••, 55••,56–61].

CHOP/Gadd153, a transcription factor induced during ER stress and subsequently activated by p38 MAP (mitogen-associated protein) kinase, may also function as an ER-stress-induced cell death modulator [6,13,62,63]. Deletion of the *CHOP* gene leads to an attenuation in the cell death usually induced by ER stress [64,65]. Although the identification of the downstream target genes that respond to CHOP/Gadd153 is still unclear, it has been suggested that Gadd153 may promote ER-stress-induced cell death by down-regulating Bcl-2 expression [65].

Another ER-stress-induced effector protein is BAP31, an ER transmembrane protein that is cleaved by caspase-8, leading to ER calcium release and subsequent uptake by mitochondria, followed by mitochondrial cytochrome *c* release, further caspase activation and apoptosis. Thus, Bap31 appears be a coordinator of cell death signals between the extrinsic pathway, the ER and the mitochondrial pathway(s) [45,66,67].

Recent data have also implicated the calcium-binding protein apoptosis-linked gene 2 (ALG-2) and valosin-containing protein (VCP) as mediators of ER-stress-induced programmed cell death (PCD). However, there is a growing realization that some such mediators may be specific for a given inducer or set of inducers: for example, ALG-2 was found to mediate ER-stress-induced apoptosis when thapsigargin, but not tunicamyin or brefeldin-A, was the inducer; VCP, however, was found to be a mediator for all three inducers [68]. Together with caspase-12, caspase-9, caspase-7, ATP and Ca^{2+} (and, potentially, other molecules), VCP and ALG-2 trigger ER-stress-induced cell death [68]. VCP also functions as a sensor of abnormally folded proteins, and has been shown to act as a cell death effector in polyglutamine-induced cell death [69,70].

In addition to the two main pathways that initiate the caspase cascade — namely, the death receptor (extrinsic) pathway, which involves caspase-8 (or caspase-10), and the mitochondrial (intrinsic) pathway, which involves caspase-9 as the apical caspase [71–73] — studies from multiple laboratories point to a caspase-12-mediated intrinsic apoptotic pathway that involves the endoplasmic reticulum and the UPR [42•,74–76,77•,78•]. Caspase-12, which is associated with the ER, is specifically involved in apoptosis that results from ER stress (at least in murine cells; whether the human caspase-12 gene actually encodes an enzymatically active caspase remains controversial [42•,68,74–76,77•,79]). Caspase-12 may be activated by *m*-calpain, a cysteine protease activated by perturbed calcium homeostasis in ER-stressed cells, or by caspase-7, which is recruited to the ER in stressed cells, or by ER-stress-activated IRE1, which recruits caspase-12 through tumor necrosis factor receptor-associated factor 2 (TRAF2) protein [75,76,80]. Caspase-12, together with caspase-9, triggers a downstream apoptotic pathway that is independent of Apaf-1, cytochrome *c* and mitochondria [77 ,78•,81]. A recent study also implicates human

caspase-4 in ER-stress-induced cell death. Caspase-4 is primarily activated in ER-stress-induced apoptosis and may function as an ER-stress-specific caspase in humans [82].

ER stress, UPR and neurodegeneration

Misfolded proteins, and the associated ER stress, are emerging as virtually constant features of neurodegenerative diseases. That UPR- and ER-stress-induced cell death could be involved in the pathogenesis of several neurodegenerative disorders (as opposed to being causally unrelated correlates) comes from several recent reports. The accumulation of misfolded proteins resulting in alterations in the structure of organelles, including the ER, has been observed in transgenic models of HD, AD and ALS, as well as in huntingtin-null mice [83–99]. Examples of such misfolded proteins, and related complexes, include the neurotoxic oligomers of the Aβ-peptide in AD [100–102]; cytoplasmic inclusions (Lewy bodies) that stain for α-synuclein, parkin and an unfolded form of the PAEL (parkin-associated endothelin receptor-like) protein [2,102–105] in PD; intracellular inclusions in degenerating neurons and glia that stain for mutant CuZnSOD [83,106,107] in murine models of ALS; and the expanded polyglutamine (poly Q) aggregates that trigger ER-stress-induced cell death in HDand other polyglutamine expansion diseases [104,105,108, 109•, 110,111]. Since these neurodegenerative diseases may be caused by specific mutant proteins that accumulate as misfolded proteins and escape degradation, it is likely that ER stress plays an important pathogenetic role in these diseases.

Thus recent studies have suggested the following: first, a role for presenilin-1 in the activation of IRE1 and induction of the UPR [112]; second, a role for GRP78 (Bip) in binding and limiting the production of Aβ peptide; and third, reduced cytotoxicity of the β-amyloid peptide in caspase-12 deficient mice, suggesting a link between the role of the UPR and ER stress in AD [75,113]. In mouse models of AD featuring the overexpression of mutant presenilin-1, the UPR is downregulated and neurons are highly susceptible to ER-stress-induced cell death [114– 121]. Neurons expressing PS1 mutations exhibit increased sensitivity to death induced by DNA damage, and the hypersensitivity to DNA damage is correlated with increased intracellular Ca^{2+} levels, induction of p53, upregulation of the Ca^{2+}-dependent protease *m*-calpain, mitochondrial membrane depolarization and activation of caspase-12 [114–117]. Another ER protein, HERP (homocysteine-induced ER-stress-responsive protein), regulates PS-mediated Aβ generation and accumulation and the formation of senile plaques and vascular Aβ deposits. These data, taken together, implicate caspases and misfolded or unfolded Aβ in UPR-induced apoptosis [122].

Several lines of transgenic mice engineered to express mutant forms of the CuZnSOD gene develop a motor neuron disease (MND) that resembles human familial amyotrophic lateral sclerosis (FALS). These mice show prominent degeneration of mitochondria and ER in spinal cord neurons [123–126]. Aggregate formation leading to extensive dilation of the ER is also observed in mouse models of ALS featuring the expression of CuZnSOD mutants, and this is not observed with the expression of wild-type CuZnSOD protein [84,86,125–127]. Furthermore, in tissue culture models, mutant CuZnSOD (but not wild-type CuZnSOD) aggregates in association with the ER and induces ER-stress-associated increases in the levels of GRP78/BiP [123]. The viability of neurons expressing the mutant CuZnSOD is protected by overexpressing heat-shock-protein 70 (HSP70), arguing that protein folding plays a role in cytotoxicity, at least in this model [128].

PD is characterized pathologically by the loss of dopaminergic neurons, primarily in the substantia nigra pars compacta, and by the presence of ubiquitinated protein deposits in the neuronal cytoplasm (Lewy bodies), as well as by protein inclusions within neurites. These deposits and inclusions contain aggregates of α-synuclein (a small presynaptic protein of

incompletely defined function), which is mutated in some of the familial cases of PD [129–133]. In a *Drosophila* model of PD, overexpression of wild-type or mutant α-synuclein triggers dopaminergic neuron cell loss that is prevented by overexpression of Hsp70 [134•]. Similarly, mutations in another protein dubbed parkin — a member of the E3 ubiquitin ligase family of proteins — result in autosomal recessive juvenile parkinsonism (ARJP) [135,136]. Overexpression of normal parkin inhibits ER-stress-induced cell death triggered by cellular parkin that is mutated in juvenile parkinsonism, suggesting that accumulation of misfolded mutant parkin (or one of the targets of its E3 ligase activity) might contribute to the selective dopaminergic neuronal cell death observed in ARJP [135–137]. One potentially critical target, a putative G-protein-coupled transmembrane polypeptide named PAEL receptor, is a parkin-binding protein, and may be a target for degradation mediated by the E3 ligase activity of parkin. Overexpression of this receptor unfolds the protein, decreasing its solubility, and results in unfolded-protein-induced cell death. A marked increase in PAEL receptor, presumably due to a defect in parkin-mediated degradation, was demonstrated in the brains of ARJP patients [136,138,139].

Toxins including rotenone, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenylpyridinium (MPP+) cause the death of dopaminergic neurons *in vitro* and *in vivo*, and are widely used to model PD. Treatment of dopaminergic cells with these drugs triggers the induction of a large number of genes involved in ER stress and the unfolded protein response, such as ER chaperones and elements of the ubiquitin-proteasome system [140,141]. These results are also compatible with the notion of a link between PD, the UPR and ER stress.

HD, a fatal autosomal-dominant neurodegenerative disease involving predominantly the caudate nucleus and the cerebral cortex, causes involuntary movements, emotional disturbance and cognitive decline. The exact mechanisms underlying neuronal death in HD are still incompletely defined; however, the molecular basis of HD has been shown to be the polyglutamine (polyQ) expansion in the N terminus of Huntingtin (Htt), a cytosolic protein expressed in almost all cells of the body. Numerous theories have been advanced to explain the selective neurodegeneration in this disease, such as the induction of mitochondrial dysfunction and subsequent excitotoxic injury, oxidative stress and apoptosis. Studies demonstrating the involvement of UPR and ER stress in trinucleotide-repeat disorders have also been reported [142]. The cytoplasmic accumulation of polyQ triggers ER stress, apparently by inhibiting the ubiquitin–proteasome system [108,110,111•]. Subsequently, ER stress activates both the TRAF2–ASK1 complex and caspase-12-mediated apoptotic pathways [108,110], and overexpression of Hsp70 suppresses polyQ toxicity [143]. Postmortem brain samples from patients with Huntington's disease show a selective decrease in ER-associated α-glucosidase and fucosyl-transferase activities in the putamen, suggesting that these changes reflect highly specific alterations in glycoprotein synthesis and processing and may contribute to the underlying pathology of these disorders [144].

Conclusions

The ER is very sensitive to changes in its environment, and such changes may lead to disruption of its normal homeostasis. A variety of environmental insults, as well as genetic diseases associated with the accumulation of misfolded proteins, can all affect the ER structure, function and integrity, leading to ER stress and contributing to the pathogenesis of different disease states. Prolonged stress leads to organelle damage and dysfunction, and ultimately triggers PCD. The accumulation of misfolded proteins seen in various neurodegenerative diseases leads to an ER stress response, irrespective of whether the misfolded proteins build up within the ER or outside the ER. Further insights into the pathways triggered by misfolded proteins, ER stress responses and cell death programs

should facilitate the development of new therapeutic strategies for neurodegenerative disorders and other disorders that feature misfolded proteins.

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Abbreviations

AD	Alzheimer's disease
ALG-2	apoptosis-linked gene 2
ALS	amyotrophic lateral sclerosis
ARJP	autosomal recessive juvenile parkinsonism
ATF6	activating transcription factor 6
eiF2α	eukaryotic translation initiation factor 2 alpha
ER	endoplasmic reticulum
GRP	glucose regulated protein
GRP78/Bip	glucose-regulated protein of 78 kilodaltons
HD	Huntington's disease
HSP70	heat-shock-protein 70
IRE-1	inositol-requiring transmembrane kinase/endoribonuclease
PAEL	parkin-associated endothelin receptor-like
PCD	programmed cell death
PD	Parkinson's disease
PERK	PKR-like ER kinase
polyQ	polyglutamine
UPR	unfolded protein response
VCP	valosin-containing protein
XBP-1	X-box-binding protein 1

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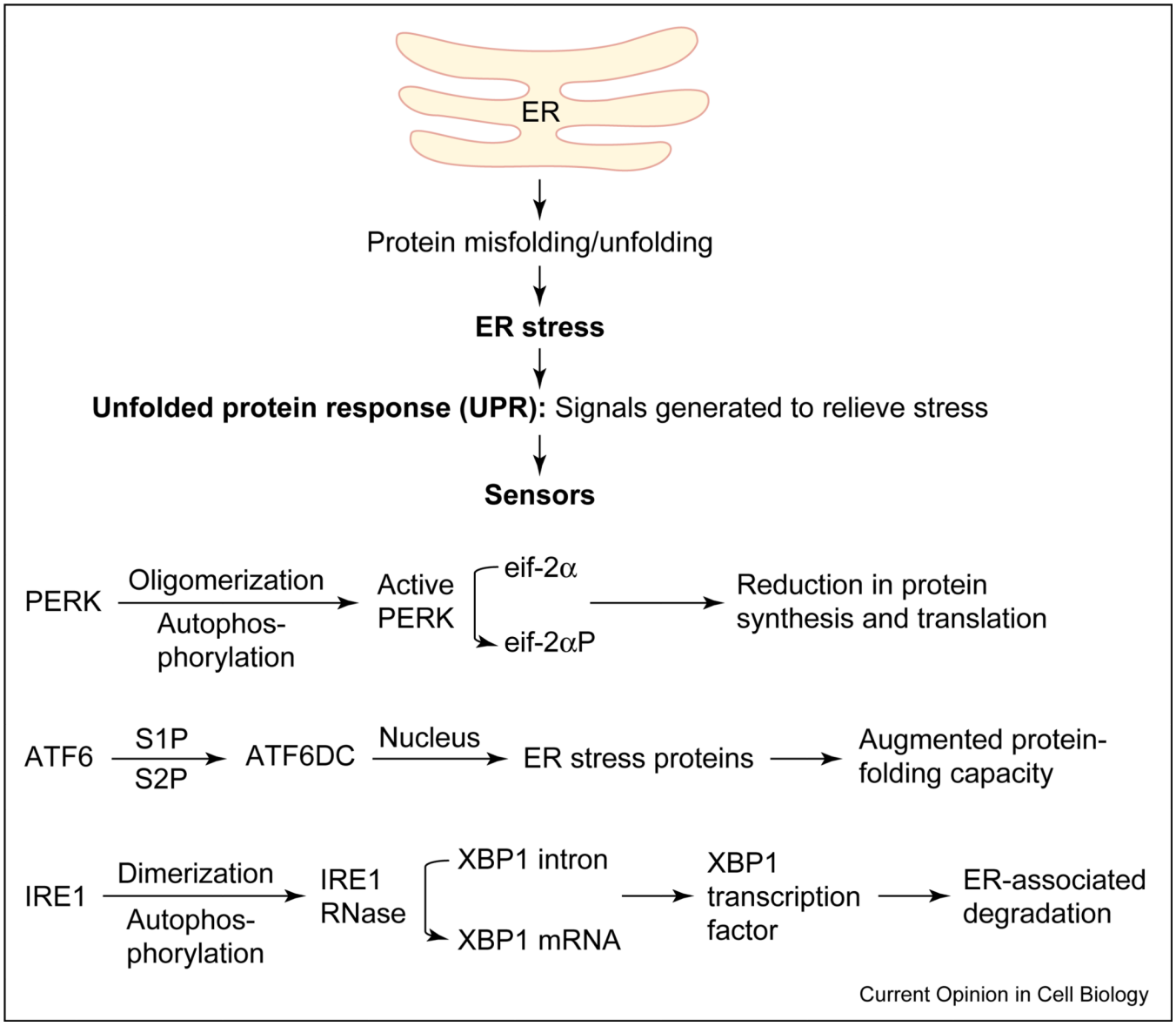

Figure 1.

Accumulation of misfolded proteins in the ER can disrupt ER function resulting in 'ER stress'. The ER responds by triggering specific signaling pathways including the UPR. The UPR is coordinately regulated by the three proximal sensors, IRE1, PERK and ATF6. The activation of all three proximal sensors results in reduction in the amount of new protein translocated into the ER lumen, increased degradation of ER-localized proteins and increased protein folding capacity of the ER. ATF6DC represents the 50kD cytosolic bZIP-containing fragment that translocates to the nucleus to activate transcription.

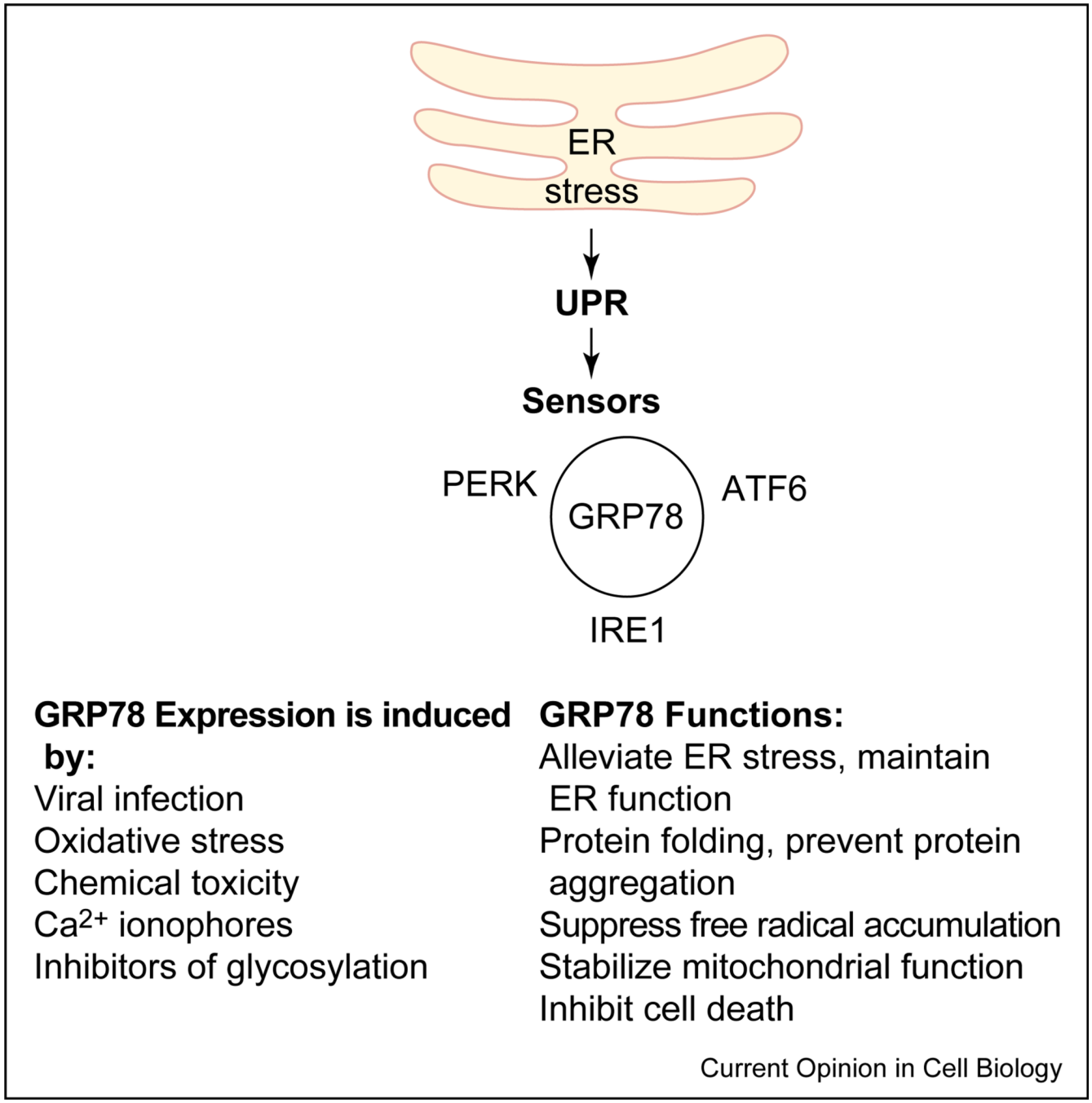

Figure 2.

The UPR is negatively regulated by GRP78/Bip, which associates with the three proximal sensors, IRE1, PERK and ATF6. GRP78 binds to the luminal domains of IRE1 and PERK and prevents their dimerization and activation. GRP78 associates with ATF6 and prevents its translocation to the Golgi for further activation. In the presence of misfolded proteins, GRP78 dissociates from the sensors and binds the misfolded proteins, thus releasing the sensors from negative inhibition. The three sensors coordinately regulate the UPR through their various signaling pathways.