Endoplasmic Reticulum Stress and Unfolded Protein Response Pathways: Potential for Treating Age-related Retinal Degeneration

Mohammad Haeri, MD, PhD; Barry E Knox, PhD

SUNY Eye Institute, Departments of Neuroscience and Physiology and Ophthalmology
SUNY Upstate Medical University, Syracuse, NY, USA

Accumulation of misfolded proteins in the endoplasmic reticulum (ER) and their aggregation impair normal cellular function and can be toxic, leading to cell death. Prolonged expression of misfolded proteins triggers ER stress, which initiates a cascade of reactions called the unfolded protein response (UPR). Protein misfolding is the basis for a variety of disorders known as ER storage or conformational diseases. There are an increasing number of eye disorders associated with misfolded proteins and pathologic ER responses, including retinitis pigmentosa (RP). Herein we review the basic cellular and molecular biology of UPR with focus on pathways that could be potential targets for treating retinal degenerative diseases.

Keywords: ER Stress; Unfolded Protein Response; Age-related Retinal Degeneration; Misfolded Protein; Protein Aggregation; Retinal Degenerative Diseases

ENDOPLASMIC RETICULUM STRESS AND PROTEIN FOLDING

The endoplasmic reticulum (ER) is the principal site for synthesis and maturation of secretory and transmembrane proteins. More than 30% of cellular proteins are synthesized in the ER.[1] Folding is the most critical step in protein synthesis. Any delay in or impairment of protein folding and processing results in accumulation of misfolded protein triggering ER stress which is a response characterized by ER distension and perturbation in ER homeostasis.[2] Accumulation of misfolded proteins and/or their aggregation are toxic to the cell and impair normal cellular function. To cope with any perturbation by unfolded or misfolded proteins, the ER induces a cascade of reactions called the unfolded protein response (UPR).[3] ER stress is the precursor of UPR, however these terms have been used interchangeably and will be used as such throughout this review.

Protein misfolding is the basis for a variety of disorders known as ER storage or conformational diseases.[4,5] However, recent studies show that UPR is activated during normal cellular events such as B-cell differentiation,[6] muscle differentiation,[7] or viral infections.[8,9] The common theme in these events which trigger the UPR response is the build-up of unfolded proteins.[10-15]

Generally, cellular responses in UPR are composed of (1) translational attenuation to prevent further production of unfolded

proteins,[16] (2) transcriptional induction of ER resident proteins (chaperones and foldases) to further assist protein folding,[17] (3) induction of ER-associated degradation (ERAD) machinery to handle misfolded proteins and reduce the burden on ER folding capacity,[18] and (4) enlargement of the ER to deal with the large load of unfolded proteins.[19] The successful execution of compensatory responses to stress by these mechanisms restores normal cell function and survival. Alternatively, irreversibly stressed cells will undergo apoptosis in response to prolonged UPR (Fig. 1).

The ER stress response is mediated by three receptors located in the ER membrane. Translational attenuation in the UPR is mediated by the double-stranded RNA-activated protein kinase (PKR)-like endoplasmic reticulum kinase (PERK) signalling pathway. PERK receptors sense the presence of unfolded proteins[20] and reduce the activity of the ribosomal initiating factor (eIF2α) by phosphorylation of its α-subunit.[16] Transcriptional activation of ER-resident proteins is mediated by activating transcription factor 6 (ATF6)[21] and inositol requiring kinase 1 (IRE1) receptors. In a similar mechanism to PERK receptors, ATF6 and IRE1 receptors sense the accumulation of misfolded proteins and induce the transcription of ER-resident proteins to assist folding and to degrade misfolded proteins. ATF6 activates the transcription of molecular chaperones such as BiP, GRP94[17] and PDI[22]. IRE1 induces the synthesis of a potent X-box-binding protein 1 (XBP1) and consequently activates
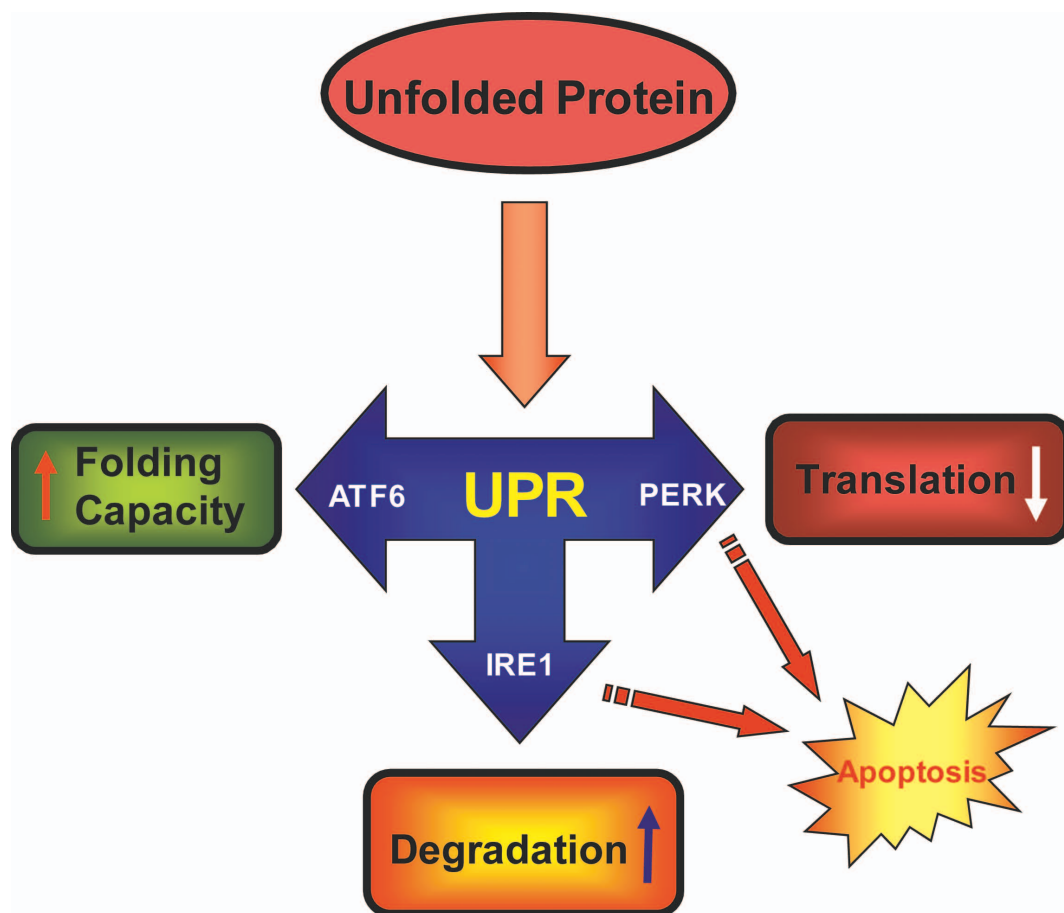
Figure 1. Major unfolded protein response (UPR) pathways. The influx of unfolded proteins in the endoplasmic reticulum (ER) induces UPR. UPR is relayed to the cell by activation of three receptors: IRE1, PERK and ATF6. Induction of these pathways starts processes to (1) decrease the load of protein by translational attenuation, (2) to increase the folding capacity of the ER, and (3) to decrease the protein load in the ER by degradation of unfolded proteins. Cells which fail to restore their normal cellular function experience prolonged activation of UPR resulting in apoptosis.

the transcription of ER associated degradation (ERAD) proteins such as EDEM.[23,24] IRE1 also activates the transcription of other UPR target genes, such as BiP, through XBP1 activation[25] (Fig. 2).

To assist protein folding in the UPR, BiP is the first target for upregulation. BiP is a molecular chaperone with high affinity for short hydrophobic peptides on the surface of unfolded proteins. The binding and releasing of these peptides from BiP assist the folding of the substrate protein.[26,27] BiP is also a sensor for unfolded proteins in the ER. An overload of unfolded proteins in the ER titrates BiP away from the luminal domains of IRE1, PERK and ATF6 receptors, which results in their further homodimerization, autophosphorylation and activation[16,20,28]. The dissociation of BiP from the ATF6 luminal domain leaves ATF6 free to be transported to the Golgi where it is cleaved to become an active transcription factor[29] (Fig. 2). Downstream UPR target genes are regulated by two distinct consensus response elements, the *cis*-acting ER stress response element (ERSE) and the unfolded protein response element (UPRE) both of which are located in the promoter of genes involved in UPR. Binding of ATF6[21] and XBP1 to these elements promotes transcription of downstream UPR genes[30,31].

The IRE1, PERK and ATF6 receptors initiate pathways, which comprise the three arms of the UPR. Located in the ER membrane, these receptors have a transmembrane domain spanning the ER membrane, a cytosolic or nucleoplasmic domain, and a luminal domain that has a binding site for BiP. IRE1 receptor is a type I transmembrane protein kinase receptor which has site-specific endoribonuclease (RNase) activity in its cytosolic domain.[32-35] IRE1 is highly conserved in eukaryotes.[28,32,33,36-38] Two types of IRE1 receptors have been found in mammals. IRE1α is ubiquitously expressed in all tissues, but the expression of the second type, IRE1β, is limited to the gut.[20,34,35,39] Deletion of IRE1α is lethal in mice; however, IRE1β$^{-/-}$ mice are viable.[20,39] The luminal domain of the IRE1 receptor binds to BiP. Accumulation of unfolded proteins in the ER, results in BiP release from the IRE1 luminal domain which in return causes

dimerization and autophosphorylation of IRE1. Phosphorylation of the cytosolic domain of the IRE1 receptor activates its RNase activity.[30,31,40-42] In mammals, XBP1 mRNA is the substrate for IRE1 endoribonuclease.[30,31,40] XBP1, a bZIP (basic region and leucine zipper)-domain-containing transcription factor of the ATF/CREB (cyclic-AMP-responsive-element-binding protein) family, binds to ERSE.[21,43] During ER stress, IRE1 endoribonuclease splices out a 26-nucleotide intron from XBP1 mRNA and creates a translational frameshift. This spliced form of XBP1 becomes an active transcription factor.[15,30,31,40] XBP1 then translocates to the nucleus and induces the transcription of genes involved in protein folding and degradation [24,40,44-48] (Fig. 2).

The PERK receptor is a type I transmembrane protein kinase receptor which is activated by ER stress with the release of BiP from its luminal domain. Release of BiP from PERK, results in its oligomerization with subsequent autophosphorylation of its cytosolic domain.[16,20,21,49] Activated PERK receptors phosphorylate the α-subunit (S51) of eIF2 (eIF2α), which inhibits 80S ribosome assembly and consequently attenuates protein synthesis/translation.[16,50,51] The inhibition of ribosomal assembly reduces the influx of newly synthesized proteins to an already saturated ER. In contrast, phosphorylation of eIF2α promotes the translation of ATF4 upon ER stress.[11,52,53] ATF4 is a transcription factor which activates the transcription of chaperones, ERAD machinery and other genes involved in the oxidative stress response and ER stress-induced apoptosis[20,54-56], such as C/EBP homologous transcription factor (CHOP), growth arrest and DNA damage gene 34 (GADD34)[20,57-59] and ATF3[58].

The ATF6 receptor is a type II transmembrane protein with a cytosolic/nucleoplasmic and an ER luminal domain.[60] Mammals have two ATF6 homologs, ATF6α and ATF6β.[61] There are two distinct ER stress-regulated Golgi localization sequences (GLS1 and GLS2) in the luminal domain of ATF6α and one GLS2 in that of ATF6β. BiP binds to GLS1 and retains the ATF6 receptor within the ER. Release of BiP from GLS1 upon ER stress results in ATF6 translocation to the
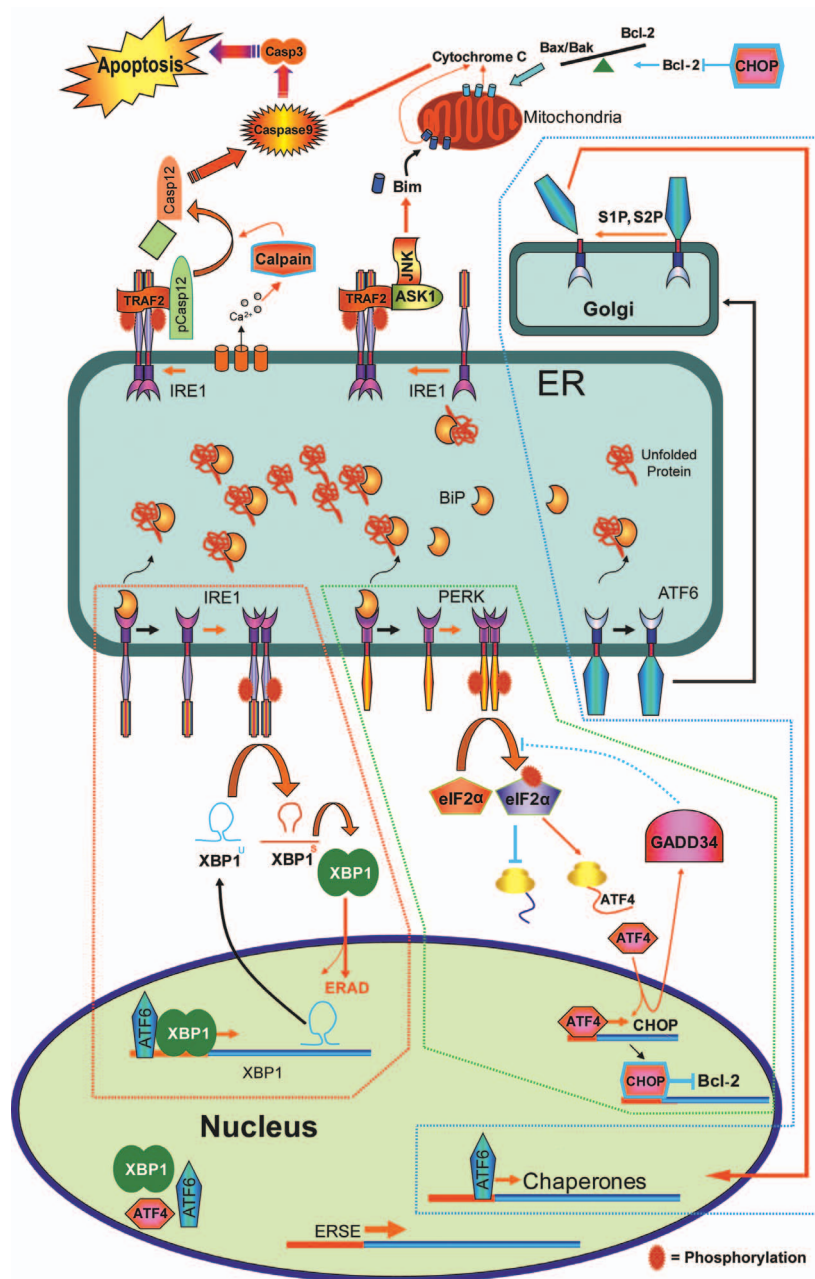
Figure 2. Unfolded protein response (UPR). The ER stress response is mediated by three receptors located in the ER membrane. The IRE1 pathway is activated by the release of BiP from IRE1 which is followed by dimerization and autophosphorylation of its cytoplasmic domain. The activated IRE1 receptor triggers its intrinsic RNase activity, which splices out a 26-nucleotide intron from XBP1 mRNA and creates a translational frameshift leading to production of an active transcription factor, XBP1. XBP1 activates the transcription of ERAD-related proteins (red-dotted area). Chronic activation of IRE1 leads to recruitment of TRAF2 followed by activation of ASK1, p38 and JNK. Activated JNK translocates to the mitochondrial membrane and promotes phosphorylation of Bim, which is associated with Bax-dependent release of cytochrome c and activation of the caspase cascade. The PERK pathway is activated by the release of BiP generating a dimerized-phosphorylated PERK enzyme which reduces the activity of the eIF2α by phosphorylation of its α-subunit. Although the phosphorylation of eIF2α generally attenuates protein synthesis/translation, it promotes the translation of ATF4 upon ER stress. ATF4 activates the transcription of chaperones, ERAD machinery and ER-stress-induced pro-apoptotic factors, such as CHOP and GADD34 and ATF3 (green-dotted area). In the ATF6 pathway, the release of BiP from the ATF6 receptor frees the receptor to be transported to the Golgi. Once in the Golgi, the cytosolic domain is cleaved by S1P and S2P, releasing a bZIP transcription factor, ATF6. ATF6 translocates to the nucleus where it activates the transcription of BiP, XBP1, CHOP and P58IPK (blue-dotted area).

Golgi.[62] The cytosolic domain of ATF6 in the Golgi is cleaved by site-1 proteases (S1P and S2P) releasing a bZIP transcription factor, ATF6.[18,29,63-65] ATF6 translocates to the nucleus where it interacts with nuclear factor-Y and XBP1, binds to ERSE and UPRE elements and activates the transcription of *BiP, XBP1, CHOP* and *P58^IPK*[18,21,66-69] (Fig. 2). Activated ATF6 also induces the expression of genes involved in protein folding and degradation.[63, 64]

PRO-APOPTOTIC PATHWAYS IN ENDOPLASMIC RETICULUM STRESS

Prolonged ER stress seems to activate IRE1α, ATF6 and PERK pathways sequentially and deactivates them in the same order.[70] If the UPR response fails to restore cellular homeostasis, the cell initiates apoptosis.[53,71,72] Prolonged ER stress-induced apoptosis is an important pathologic element of neurodegenerative diseases, diabetes, renal diseases and atherosclerosis.[73] Generally, apoptosis is known as the nuclear form of programmed cell death (PCD). Other types of PCDs are autophagic (type II)[74-76] and cytoplasmic (type III) PCD[75-78]. The PCD associated with UPR is probably the nuclear form. Four known pro-apoptotic pathways have been implicated in ER-stress mediated apoptosis; 1) IRE1α-mediated activation of ASK1 (apoptosis signal-regulating kinase 1), 2) caspase-12[79], 3) PERK/eIF2α induction of CHOP, and 4) BAK/BAX-induced Ca^{2+} release from the ER [35,80].

Apoptosis signalling is mediated by two major pathways. The extrinsic pathway is triggered by self-association of membrane receptors and recruitment of caspase-9 which results in initiation of a caspase cascade and finally apoptosis. The intrinsic pathway is triggered by dominance of pro-apoptotic over anti-apoptotic members of the Bcl-2 family. Anti-apoptotic members of the Bcl-2 family are Bcl-2 and Bcl-X$_L$, and pro-apoptotic members are BH3-only classes including Bid and Bim as well as multidomain groups, such as Bax and Bak. A variety of apoptotic stimuli promote translocation of Bax and Bak from the cytosol into the mitochondria resulting in release of cytochrome c and activation of caspases.[81]

The IRE1/TRAF2/ASK1/JNK pathway is considered the dominant pro-apoptotic pathway in ER stress. It has been shown that IRE1α is able to recruit TNF receptor-associated factor 2 (TRAF2) to its cytosolic domain. TRAF2 can subsequently activate apoptosis signal-regulating kinase (ASK) 1, p38 and finally c-Jun amino-terminal kinase (JNK).[20,28,82] Co-expression of ASK1 and JNK results in phosphorylation and inactivation of Bcl-2.[83] Activated JNK has been shown to translocate to the mitochondrial membrane[84] and promote phosphorylation of Bim, which is associated with Bax-dependent release of cytochrome c[85,86]. ASK1 can also be activated by reactive oxygen species (ROS) initiating apoptosis. ASK1 is inhibited by thioredoxin (TDX), a protein which inactivates ROS, until accumulation of ROS causes oxidation of TDX, thereby disinhibition of ASK1.[28,87] IRE1α can also induce apoptosis through 1) interaction of the TNF receptor 1 (TNFR1) with TRAF2/ASK1 and subsequent activation of JNK and through 2) interaction of TRAF2 and the inhibitor of κB-kinase (IKK) which leads to activation of nuclear factor κB[88,89].

The PERK/ATF4/CHOP pathway is the second pro-apoptotic mechanism triggered by prolonged ER stress[35,90,91]. CHOP is minimally expressed under non-stress conditions; however, its expression is moderately increased upon ER stress. CHOP expression has been shown to induce cell cycle arrest and/or apoptosis.[35,80,90-94] Transcriptional activation of CHOP is mediated by the IRE1, PERK or ATF6[18,20,35,80,95] pathways. CHOP is also activated post-translationally via p38 MAP kinase phosphorylation.[90] It has been shown that CHOP expression sensitizes the cell to apoptosis by downregulation of BCL-2 and/or depletion of glutathione leading to accumulation of ROS in the cell[93] (Fig. 2). CHOP expression promotes pro-apoptotic factors such as DR5, TRB3, BIM and GADD34 [96-99]. Association of CHOP with ER stress-induced apoptosis has been reported in diabetes,[80,99] renal dysfunction,[35] atherosclerosis,[100] cardiac overload,[101] colitis,[102] and Parkinson's disease[103]. CHOP is a major pro-apoptotic factor in ER stress and its deletion promotes cell survival. Several

therapeutic approaches have targeted the PERK-CHOP pathway in a mouse model of ER stress to inhibit apoptosis. Blocking the phosphorylation of eIF2α by Salubrinal promoted cell survival in these mouse models implicated with ER stress.[104]

The PERK pathway is also induced by accumulation of ROS[105,106]. ROS are small molecules or free radicals (atoms, molecules or ions with unpaired electrons or open shelf configuration) formed by molecular oxygen.[107] ROS have been linked to mediators of inflammation.[108] Protein folding is an energy consuming process through which the formation of disulfide bonds is required for correct folding of some proteins.[105, 106] To deal with ROS formed during protein folding in ER stress, the PERK pathway induces the transcription of glutathione *S*-transferase, NAD(P)H:quinone oxidoreductase-1, γ-glutamate cysteine ligase, and hemeoxygenase-1 to protect the cell from oxidative stress.[44,54,109-124] Oxidative stress is believed to play an important role in age-related macular degeneration (AMD), retinitis pigmentosa (RP) and other ocular diseases.[125]

Some evidence suggests a role for caspase-12 as another pro-apoptotic pathway in ER stress.[126] Caspase-12 is a member of the group I family of caspases (also known as ICE-like caspases and consists of caspase-1, 4, 5, 11, and 13). Caspase-12 is localized on the cytoplasmic side of the ER membrane[127] and is associated with ER stress-mediated apoptosis[79]. It has been shown that activated caspase-12 translocates to the cytosol and subsequently activates caspase-9 and caspase-3.[128] Caspase-12 activation by amyloid β (Aβ) peptide through calpain has been shown in primary neurons.[79] In humans, the functional caspase-12 homologue is not expressed due to a mutation[129]; therefore, other caspases may play a role in apoptosis.[130]

NEURODEGENERATIVE DISEASES AND UPR

Retinal degeneration is one of the leading causes of blindness in humans. The current hypothesis proposed for retinal degeneration elicited by ER stress is the activation of UPR pathways. Some types of retinal degenerations share similar pathological origins to neurodegenerative diseases. These include protein misfolding, aggregate formation and activation of protein degradation machinery. Furthermore, involvement of UPR has been suggested by cell culture studies and animal models.[11,131] There are a few similarities found in the origins of neurodegenerative diseases and those found in retinal degenerations. A better understanding of the pathogenesis of neurodegenerative diseases could shed light on the molecular pathology of eye diseases. Neurodegenerative diseases are chronic conditions originating from mutations in genes that lead to neural cell death. In many neurodegenerative diseases, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple sclerosis (MS) and polyglutamine diseases (which result from expansion of a polyglutamine repeat), the major molecular pathology is the formation of protein aggregates.[132] Aggregate formation can limit or inhibit the capacity of the cell for ER-associated protein degradation (ERAD) by proteasomes. Failure of the cell to degrade misfolded aggregates induces UPR and eventually neural cell death.[133, 134]

Alzheimer's disease is among the well known neurodegenerative diseases in which the PERK-EIF2α pathway is activated.[14,135-138] Juvenile-onset Parkinson's disease is another example of UPR-driven cell death in which mutations in Parkin, an E3 ubiquitin ligase causes ER stress.[139,140] The expression of wild type Parkin is induced by ER stress to clear misfolded proteins through ERAD.[141] The overexpression of wild type Parkin promotes survival in cells expressing mutant α-synuclein or those treated with ER stress-inducing agents.[140-142] Evidence of ER stress has been reported in other forms of neurodegenerative diseases such as ALS [134], Huntington's disease[143-147] and diseases associated with Prions such as transmissible spongiform encephalopathies of Creutzfeldt-Jakob disease and Kuru[148].

ROLE OF UPR IN EYE DISEASES

UPR is a response to ER stress and is implemented differently depending on cell

type, nature of ER stress, its magnitude and duration.[89, 149, 150] UPR can serve to protect the cell by re-establishing ER homeostasis or it can trigger apoptosis under severe or chronic ER stress.[151,152] The presence of misfolded protein is the trigger for induction of UPR. A growing number of reports suggest that misfolded proteins play a role in the pathogenesis of several eye disorders.[153] Several studies have demonstrated the association of misfolded protein and UPR in RP. UPR might also be involved in the conversion of dry AMD to the wet form through angiogenesis stimulated by the vascular endothelial growth factor (VEGF) released from retinal pigmented epithelium (RPE) cells.[154] UPR has also been implicated in the early onset form of Fuchs endothelial corneal dystrophy (FECD) which is the leading indication for corneal transplantation.[155] Among other diseases that might be linked to ER stress, investigators have reported the activation of UPR by cataract-associated αA-crystallin[156] and collagen IV[157] mutations in animal models. Moreover, possible involvement of ER stress has been proposed in adult-onset primary open angle glaucoma (POAG).[158] Mutations in carbonic anhydrase (CA) IV, a highly expressed enzyme in the choriocapillaris of the human eye, are associated with the RP17 form of autosomal dominant RP due to accumulation of unfolded proteins in the ER.[159-161] Besides the retina, other neuronal cells are subject to induction of UPR as shown in several neurodegenerative diseases. ALS,[162] Parkinson's, Huntington's and Alzheimer's disease, and prion-related disorders are among degenerative diseases associated with UPR.[163]

The association of UPR and visual impairment has been well described in animal models of RP. Among the over 40 genes causing RP, the most common forms of autosomal dominant RP are due to mutations in rhodopsin. Mutations in rhodopsin cause the formation of misfolded proteins which induce ER stress. Enormous amounts of rhodopsin are made every day and the overload of photoreceptors with misfolded rhodopsin triggers UPR. The induction of UPR has been observed in several animal models of RP.[70, 164-166]

UPR IN RETINAL DEGENERATION: POTENTIAL THERAPEUTIC APPROACHES

Photoreceptors synthesize a large amount of protein every day indicating the critical role for ER function in these cells. Altered expression of some molecular chaperones, the major component of protein folding and quality control in the ER, was found in proteomics of a murine model of retinal degeneration.[11,167-169] Some mutations in rhodopsin, which result in the production of misfolded proteins, lead to retinitis pigmentosa (RP). These types of RPs have been classified as ER storage diseases.[3] The expression level of ATF6, phosphorylated eIF2α, and CHOP in a rat model of RP expressing rhodopsin-P23H mutation were higher as compared to control animals. Overexpression of BiP in the P23H rat model led to a decrease in CHOP levels and apoptosis, and an increase in the amplitude of the electroretinogram[164] which indicates that increased folding capacity in cells may inhibit apoptosis. The expression of ER stress markers, XBP1 and Hrd1, was increased in a fly model of RP expressing mutant Rh1, the equivalent of rhodopsin in vertebrates. It was demonstrated that reduced function of ERAD led to an increase in mutant Rh1 which suggest its role in degradation of mutant opsin. On the other hand, overexpression of the ERAD machinery reduced the levels of mutant Rh1 and markers of ER stress.[165] These reports demonstrated induction of UPR in animal models of retinal degeneration. They also exhibited a reduction in apoptosis by overexpression of chaperones, such as BiP.

Several therapeutical approaches to alleviate retinal degeneration targeted protein folding by using chemical chaperones.[170-172] Chemical chaperones are small molecules which assist protein folding by non-covalent interactions with partially folded or misfolded proteins.[64,172-176] Protein synthesis is an energy consuming process which is assisted and monitored by several proteins mostly residing in the ER. Among assistant proteins, chaperones stabilize partially folded proteins and bind to exposed hydrophobic surfaces to direct a forming protein to its native state. Failure to

adopt the native conformation will target the misfolded protein to ER-associated degradation machinery to prevent aggregate formation.[170] However, this folding assistance and quality control might become overwhelmed due to other cellular insults such as oxidative stress, hypoxia, altered calcium homeostasis or vastly expressed inherently misfolded protein. To cope with this stress, the ER initiates a compensatory cascade of responses, i.e. the UPR,[177] which is initially a survival response that reduces the general translation of proteins to alleviate the burden of protein folding on the ER, upregulates chaperones to facilitate protein folding and induces ER-associated degradation machinery. Failure of adopted strategies to recover from stress leads to induction of apoptosis to eliminate injured cell.[137,167,178] Several neurodegenerative diseases are associated with misfolded proteins and consequently ER stress.[11,131,137, 178]

Recent studies have demonstrated facilitated protein folding by pharmacological chaperones in models of RP. Some forms of RP are associated with misfolding of mutant rhodopsin, aggregate formation and targeted degradation by the ubiquitin proteasome system. Investigators studying P23H, the most common mutation found in rhodopsin, reported that 11-cis-7-ring retinal can promote proper folding, glycosylation and localization of P23H to the cell surface.[179-181] Rescue of misfolded P23H was achieved in another study by cotransfection of P23H with Hsp70, β-synuclein, or γ-synuclein chaperones in P661W photoreceptor cells and resulted in the formation of fewer inclusion bodies.[182]

Compounds known as chemical chaperones[183,184] such as tauroursodeoxy-cholic acid (TUDCA) and 4-phenyl butyric acid, have origins in traditional Chinese medicine and have been used in humans for a variety of diseases including RP. Although some beneficial effects have been demonstrated, the definitive effect of chemical chaperones to inhibit ER stress-induced apoptosis has not been proven.[185-187]

Several investigators have shown the effectiveness of a high-throughput screen for chemical chaperones to find a potent protein aggregate inhibitor. Accordingly, yeast cells expressing Htt-103Q-EGFP (*Huntington* gene with extended polyglutamine fused to EGFP) were generated and demonstrated poor growth and low expression of the fusion protein. These cells were then treated with a library consisting of 16,000 different compounds and screened for restoration of cell growth and expression of fusion protein (Htt-103Q-EGFP). After finding effective compounds from the library, investigators examined the effect of hit compounds in the mouse and Drosophila model of Huntington's disease.[11] Future studies need to uncover the extent to which the UPR is induced in retinal degenerative diseases. A better understanding of the role of timing in the induction of UPR elements is crucial to target pro-apoptotic factors. High-throughput studies will play a major role in finding mechanisms of retinal degeneration and potential therapeutic compounds.

Acknowledgments

Conflicts of Interest

None.

REFERENCES

1. Ghaemmaghami S, Huh WK, Bower K, Howson RW, Belle A, Dephoure N, et al. Global analysis of protein expression in yeast. *Nature* 2003;425:737-741.

2. Tabas I, Ron D. Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. *Nat Cell Biol* 2011;13:184-190.

3. Schroder M, Kaufman RJ. The mammalian unfolded protein response. *Annu Rev Biochem* 2005;74:739-789.

4. Fewell SW, Travers KJ, Weissman JS, Brodsky JL. The action of molecular chaperones in the early secretory pathway. *Annu Rev Genet* 2001;35:149-191.

5. Ellgaard L, Molinari M, Helenius A. Setting the standards: quality control in the secretory pathway. *Science* 1999;286:1882-1888.

6. Reimold AM, Iwakoshi NN, Manis J, Vallabhajosyula P, Szomolanyi-Tsuda E, Gravallese EM, et al. Plasma cell differentiation requires the transcription factor XBP-1. *Nature* 2001;412:300-307.

7. Nakanishi K, Sudo T, Morishima N. Endoplasmic reticulum stress signaling transmitted by ATF6 mediates apoptosis during muscle development. *J Cell Biol* 2005;169:555-560.

8. Benali-Furet NL, Chami M, Houel L, De Giorgi F, Vernejoul F, Lagorce D, et al. Hepatitis C virus core triggers apoptosis in liver cells by inducing ER stress and ER calcium depletion. *Oncogene* 2005;24:4921-4933.

9. Yamazaki H, Nakata T, Okada Y, Hirokawa N. KIF3A/B: a heterodimeric kinesin superfamily protein that works as a microtubule plus end-directed motor for membrane organelle transport. *J Cell Biol* 1995;130:1387-1399.

10. Shen X, Zhang K, Kaufman RJ. The unfolded protein response-a stress signaling pathway of the endoplasmic reticulum. *J Chem Neuroanat* 2004;28:79-92.

11. Zhang X, Smith DL, Meriin AB, Engemann S, Russel DE, Roark M, et al. A potent small molecule inhibits polyglutamine aggregation in Huntington's disease neurons and suppresses neurodegeneration in vivo. *Proc Natl Acad Sci U S A* 2005;102:892-897.

12. Patil C, Walter P. Intracellular signaling from the endoplasmic reticulum to the nucleus: the unfolded protein response in yeast and mammals. *Curr Opin Cell Biol* 2001;13:349-355.

13. Forman MS, Lee VM, Trojanowski JQ. 'Unfolding' pathways in neurodegenerative disease. *Trends Neurosci* 2003;26:407-410.

14. Niwa M, Sidrauski C, Kaufman RJ, Walter P. A role for presenilin-1 in nuclear accumulation of Ire1 fragments and induction of the mammalian unfolded protein response. *Cell* 1999;99:691-702.

15. Harding HP, Calfon M, Urano F, Novoa I, Ron D. Transcriptional and translational control in the Mammalian unfolded protein response. *Annu Rev Cell Dev Biol* 2002;18:575-599.

16. Harding HP, Zhang Y, Ron D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature* 1999;397:271-274.

17. Gething MJ, Sambrook J. Protein folding in the cell. *Nature* 1992;355:33-45.

18. Yoshida H, Okada T, Haze K, Yanagi H, Yura T, Mori K. ATF6 activated by proteolysis directly binds in the presence of NF-Y (CBF) to the cis-acting element responsible for the mammalian unfolded protein response. *Mol Cell Biol* 2000;20:6755-6767.

19. Selye H. The nature of stress. *Basal Facts* 1985;7:3-11.

20. Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, Harding HP, et al. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. *Science* 2000;287:664-666.

21. Yoshida H, Haze K, Yanagi H, Yura T, Mori, K. Identification of the cis-acting endoplasmic reticulum stress response element responsible for transcriptional induction of mammalian glucose- regulated proteins: Involvement of basic leucine zipper transcription factors. *J Biol Chem* 1998;273:33741-33749.

22. Dorner AJ, Wasley LC, Raney P, Haugejorden S, Green M, Kaufman RJ. The stress response in Chinese hamster ovary cells. Regulation of ERp72 and protein disulfide isomerase expression and secretion. *J Biol Chem* 1990;265:22029-22034.

23. Hosokawa N, Wada I, Hasegawa K, Yorihuzi T, Tremblay LO, Herscovics A, et al. A novel ER alpha-mannosidase-like protein accelerates ER-associated degradation. *EMBO Rep* 2001;2:415-422.

24. Yoshida H, Matsui T, Hosokawa N, Kaufman RJ, Nagata K, Mori K. A time-dependent phase shift in the mammalian unfolded protein response. *Dev Cell* 2003;4:265-271.

25. Travers KJ, Patil CK, Wodicka L, Lockhart DJ, Weissman JS, Walter P. Functional and genomic analyses reveal an essential coordination between the unfolded protein response and ER-associated degradation. *Cell* 2000;101:249-258.

26. Blond-Elguindi S, Cwirla SE, Dower WJ, Lipshutz RJ, Sprang SR, Sambrook JF, et al. Affinity panning of a library of peptides displayed on bacteriophages reveals the binding specificity of BiP. *Cell* 1993;75:717-728.

27. Flynn GC, Pohl J, Flocco MT, Rothman JE. Peptide-binding specificity of the molecular chaperone BiP. *Nature* 1991;353:726-730.

28. Wolfrum U, Schmitt A. Rhodopsin transport in the membrane of the connecting cilium of mammalian photoreceptor cells. *Cell Motil Cytoskeleton* 2000;46:95-107.

29. Young JE, Albert AD. Transducin binding in bovine rod outer segment disk membranes of different age/spatial location. *Exp Eye Res* 2000;70:809-812.

30. Shen X, Ellis RE, Lee K, Liu CY, Yang K, Solomon A, et al. Complementary signaling pathways regulate the unfolded protein response and are required for C. elegans development. *Cell* 2001;107:893-903.

31. Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell* 2001;107:881-891.

32. Mori K, Ma W, Gething MJ, Sambrook J. A transmembrane protein with a cdc2+/CDC28-related kinase activity is required for signaling from the ER to the nucleus. *Cell* 1993;74:743-756.

33. Nikawa J, Yamashita S. IRE1 encodes a putative protein kinase containing a membrane-spanning domain and is required for inositol phototrophy in Saccharomyces cerevisiae. *Mol Microbiol* 1992;6:1441-1446.

34. Tirasophon W, Welihinda AA, Kaufman RJ. A stress response pathway from the endoplasmic reticulum to the nucleus requires a novel bifunctional protein kinase/endoribonuclease (Ire1p) in mammalian cells. *Genes Dev* 1998;12:1812-1824.

35. Zinszner H, Kuroda M, Wang X, Batchvarova N, Lightfoot RT, Remotti H, et al. CHOP is implicated in programmed cell death in response to impaired function of the endoplasmic reticulum. *Genes Dev* 1998;12:982-995.

36. Cox JS, Shamu CE, Walter P. Transcriptional induction of genes encoding endoplasmic reticulum resident proteins requires a transmembrane protein kinase. *Cell* 1993;73:1197-1206.

37. Okushima Y, Koizumi N, Yamaguchi Y, Kimata Y, Kohno K, Sano H. Isolation and characterization of a putative transducer of endoplasmic reticulum stress in Oryza sativa. *Plant Cell Physiol* 2002;43:532-539.

38. Koizumi N, Martinez IM, Kimata Y, Kohno K, Sano H, Chrispeels MJ. Molecular characterization of two Arabidopsis Ire1 homologs, endoplasmic reticulum-located transmembrane protein kinases. *Plant Physiol* 2001;127:949-962.

39. Bertolotti A, Wang X, Novoa I, Jungreis R, Schlessinger K, Cho JH, et al. Increased sensitivity to dextran sodium sulfate colitis in IRE1beta-deficient mice. *J Clin Invest* 2001;107:585-593.

40. Mikami A, Tynan SH, Hama T, Luby-Phelps K, Saito T, Crandall JE, et al. Molecular structure of cytoplasmic dynein 2 and its distribution in neuronal and ciliated cells. *J Cell Sci* 2002;115:4801-4808.

41. Rosenbaum JL, Witman GB. Intraflagellar transport. *Nat Rev Mol Cell Biol* 2002;3:813-825.

42. Shamu CE, Walter P. Oligomerization and phosphorylation of the Ire1p kinase during intracellular signaling from the endoplasmic reticulum to the nucleus. *EMBO J* 1996;15:3028-3039.

43. Clauss IM, Chu M, Zhao JL, Glimcher LH. The basic domain/leucine zipper protein hXBP-1 preferentially binds to and transactivates CRE-like sequences containing an ACGT core. *Nucleic Acids Res* 1996;24:1855-1864.

44. Lee JM, Calkins MJ, Chan K, Kan YW, Johnson, JA. Identification of the NF-E2-related factor-2-dependent genes conferring protection against oxidative stress in primary cortical astrocytes using oligonucleotide microarray analysis. *J Biol Chem* 2003;278:12029-12038.

45. Oda Y, Okada T, Yoshida H, Kaufman RJ, Nagata K, Mori K. Derlin-2 and Derlin-3 are regulated by the mammalian unfolded protein response and are required for ER-associated degradation. *J Cell Biol* 2006;172:383-393.

46. Hollien J, Weissman JS. Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. *Science* 2006;313:104-107.

47. Pirot P, Naamane N, Libert F, Magnusson NE, Ørntoft TF, Cardozo AK, et al. Global profiling of genes modified by endoplasmic reticulum stress in pancreatic beta cells reveals the early degradation of insulin mRNAs. *Diabetologia* 2007;50:1006-1014.

48. Molinari M, Sitia R. The secretory capacity of a cell depends on the efficiency of endoplasmic reticulum-associated degradation. *Curr Top Microbiol Immunol* 2005;300:1-15.

49. Watanabe N, Miyake Y, Wakabayashi T, Usukura J. Periciliary structure of developing rat photoreceptor cells. A deep etch replica and freeze substitution study. *J Electron Microsc (Tokyo)* 1999;48:929-935.

50. Kimball SR. Eukaryotic initiation factor eIF2. *Int J Biochem Cell Biol* 1999;31:25-29.

51. Wek RC, Cavener DR. Translational control and the unfolded protein response. *Antioxid Redox Signal* 2007;9:2357-2371.

52. Hinnebusch AG. Translational regulation of yeast GCN4. A window on factors that control initiator-tRNA binding to the ribosome. *J Biol Chem* 1997;272:21661-21664.

53. Yaman I, Fernandez J, Liu H, Caprara M, Komar AA, Koromilas AE, et al. The zipper model of translational control: A small upstream ORF is the switch that controls structural remodeling of an mRNA leader. *Cell* 2003;113:519-531.

54. Jousse C, Oyadomari S, Novoa I, Lu P, Zhang Y, Harding HP, et al. Inhibition of a constitutive translation initiation factor 2alpha phosphatase, CReP, promotes survival of stressed cells. *J Cell Biol* 2003;163:767-775.

55. Scheuner D, Song B, McEwen E, Liu C, Laybutt R, Gillespie P, et al. Translational control is required for the unfolded protein response and in vivo glucose homeostasis. *Mol Cell* 2001;7:1165-1176.

56. Vattem KM, Wek RC. Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. *Proc Natl Acad Sci U S A* 2004;101:11269-11274.

57. Zou Q, Bennion BJ, Daggett V, Murphy KP. The molecular mechanism of stabilization of proteins by TMAO and its ability to counteract the effects of urea. *J Am Chem Soc* 2002;124:1192-1202.

58. Jiang HY, Wek SA, McGrath BC, Lu D, Hai T, Harding HP, et al. Activating transcription factor 3 is integral to the eukaryotic initiation factor 2 kinase stress response. *Mol Cell Biol* 2004;24:1365-1377.

59. Okada T, Yoshida H, Akazawa R, Negishi M, Mori K. Distinct roles of activating transcription factor 6 (ATF6) and double-stranded RNA-activated protein

kinase-like endoplasmic reticulum kinase (PERK) in transcription during the mammalian unfolded protein response. *Biochem J* 2002;366:585-594.

60. Pahl HL, Baeuerle PA. A novel signal transduction pathway from the endoplasmic reticulum to the nucleus is mediated by transcription factor NF-kappa B. *EMBO J* 1995;14:2580-2588.

61. Haze K, Okada T, Yoshida H, Yanagi H, Yura T, Negishi M, et al. Identification of the G13 (cAMP-response-element-binding protein-related protein) gene product related to activating transcription factor 6 as a transcriptional activator of the mammalian unfolded protein response. *Biochem J* 2001;355:19-28.

62. Shen J, Chen X, Hendershot L, Prywes R. ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. *Dev Cell* 2002;3:99-111.

63. Yamamoto K, Sato T, Matsui T, Sato M, Okada T, Yoshida H, et al. Transcriptional induction of mammalian ER quality control proteins is mediated by single or combined action of ATF6 alpha and XBP1. *Dev Cell* 2007;13:365-376.

64. Wu J, Rutkowski DT, Dubois M, Swathirajan J, Saunders T, Wang J, et al. ATF6 alpha optimizes long-term endoplasmic reticulum function to protect cells from chronic stress. *Dev Cell* 2007;13:351-364.

65. Nadanaka S, Okada T, Yoshida H, Mori K. Role of disulfide bridges formed in the luminal domain of ATF6 in sensing endoplasmic reticulum stress. *Mol Cell Biol* 2007;27:1027-1043.

66. Kokame K, Kato H, Miyata T. Identification of ERSE-II, a new cis-acting element responsible for the ATF6-dependent mammalian unfolded protein response. *J Biol Chem* 2001;276:9199-9205.

67. Wang Y, Shen J, Arenzana N, Tirasophon W, Kaufman RJ, Prywes R. Activation of ATF6 and an ATF6 DNA binding site by the endoplasmic reticulum stress response. *J Biol Chem* 2000;275:27013-27020.

68. Yamamoto K, Yoshida H, Kokame K, Kaufman RJ, Mori K. Differential contributions of ATF6 and XBP1 to the activation of endoplasmic reticulum stress-responsive cis-acting elements ERSE, UPRE and ERSE-II. *J Biochem* 2004;136:343-350.

69. van Huizen R, Martindale JL, Gorospe M, Holbrook NJ. P58IPK, a novel endoplasmic reticulum stress-inducible protein and potential negative regulator of eIF2alpha signaling. *J Biol Chem* 2003;278:15558-15564.

70. Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, Panning B, et al. IRE1 signaling affects cell fate during the unfolded protein response. *Science* 2007;318:944-949.

71. Kadowaki H, Nishitoh H, Ichijo H. Survival and apoptosis signals in ER stress: the role of protein kinases. *J Chem Neuroanat* 2004;28:93-100.

72. Breckenridge DG, Germain M, Mathai JP, Nguyen M, Shore GC. Regulation of apoptosis by endoplasmic reticulum pathways. *Oncogene* 2003;22:8608-8618.

73. Kaufman RJ. Orchestrating the unfolded protein response in health and disease. *J Clin Invest* 2002;110:1389-1398.

74. Lockshin RA, Williams CM. Programmed cell death. II. Endocrine potentiation of the breakdown of the intersegmental muscles of silkmoths. *J Insect Physiol* 1964;10:643-649.

75. Clarke PGH. Developmental cell death: morphological diversity and multiple mechanisms. *Anat Embryol (Berl)* 1990;181:195-213.

76. Cunningham TJ. Naturally occurring neuron death and its regulation by developing neural pathways. *Int Rev Cytol* 1982;74:163-186.

77. Schweichel JU, Merker HJ. The morphology of various types of cell death in prenatal tissues. *Teratology* 1973;7:253-266.

78. Oppenheim RW. Naturally-occurring cell death during neural development. *Trends Neurosci* 1985;8:487-493.

79. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yanker BA, et al. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. *Nature* 2000;403:98-103.

80. Oyadomari S, Koizumi A, Takeda K, Gotoh T, Akira S, Araki E, et al. Targeted disruption of the Chop gene delays endoplasmic reticulum stress-mediated diabetes. *J Clin Invest* 2002;109:525-532.

81. Wei MC, Zong WX, Cheng EH, Lindsten T, Panoutsakopoulou V, Ross AJ, et al. Proapoptotic BAX and BAK: a requisite gateway to mitochondrial dysfunction and death. *Science* 2001;292:727-730.

82. Nishitoh H, Matsuzawa A, Tobiume K, Saegusa K, Takeda K, Inoue K, et al. ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. *Genes Dev* 2002;16:1345-1355.

83. Yamamoto K, Ichijo H, Korsmeyer SJ. BCL-2 is phosphorylated and inactivated by an ASK1/Jun N-terminal protein kinase pathway normally activated at G2/M. *Mol Cell Biol* 1999;19:8469-8478.

84. Aoki H, Kang PM, Hampe J, Yoshimura K, Noma T, Matsuzaki M, et al. Direct activation of mitochondrial apoptosis machinery by c-Jun N-terminal kinase in adult cardiac myocytes. *J Biol Chem* 2002;277:10244-10250.

85. Lei K, Davis RJ. JNK phosphorylation of Bim-related members of the Bcl2 family induces Bax-dependent apoptosis. *Proc Natl Acad Sci U S A* 2003;100:2432-2437.

86. Putcha GV, Le S, Frank S, Besirli CG, Clark K, Chu B, et al. JNK-mediated BIM phosphorylation potentiates BAX-dependent apoptosis. *Neuron* 2003;38:899-914.

87. Tobiume K, Saitoh M, Ichijo H. Activation of apoptosis signal-regulating Kinase 1 by the stress-induced activating phosphorylation of pre-formed oligomer. *J Cell Physiol* 2002;191:95-104.

88. Yang Q, Kim YS, Lin Y, Lewis J, Neckers L, Liu ZG. Tumour necrosis factor receptor 1 mediates endoplasmic reticulum stress-induced activation of the MAP kinase JNK. *EMBO Rep* 2006;7:622-627.

89. Zhao C, Lu S, Zhou X, Zhang X, Zhao K, Larsson C. A novel locus (RP33) for autosomal dominant retinitis pigmentosa mapping to chromosomal region 2cen-q12.1. *Hum Genet* 2006;119:617-623.

90. Wang XZ, Lawson B, Brewer JW, Zinszner H, Sanjay A, Mi LJ, et al. Signals from the stressed endoplasmic reticulum induce C/EBP-homologous protein (CHOP/GADD153). *Mol Cell Biol* 1996;16:4273-4280.

91. Nishiguchi KM, Friedman JS, Sandberg MA, Swaroop A, Berson EL, Dryja TP. Recessive NRL mutations in patients with clumped pigmentary retinal degeneration and relative preservation of blue cone function. *Proc Natl Acad Sci U S A* 2004;101:17819-17824.

92. Barone MV, Crozat A, Tabaee A, Philipson L, Ron D. CHOP (GADD153) and its oncogenic variant, TLS-CHOP, have opposing effects on the induction of G1/S arrest. *Genes Dev* 1994;8:453-464.

93. McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ. Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state. *Mol Cell Biol* 2001;21:1249-1259.

94. Southwood CM, Garbern J, Jiang W, Gow A. The unfolded protein response modulates disease severity in pelizaeus-merzbacher disease. *Neuron* 2002;36:585-596.

95. Yan W, Frank CL, Korth MJ, Sopher BL, Novoa I, Ron D, et al. Control of PERK eIF2alpha kinase activity by the endoplasmic reticulum stress-induced molecular chaperone P58IPK. *Proc Natl Acad Sci U S A* 2002;99:15920-15925.

96. Ohoka N, Yoshii S, Hattori T, Onozaki K, Hayashi H. TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. *EMBO J* 2005;24:1243-1255.

97. Yamaguchi H, Wang HG. CHOP is involved in endoplasmic reticulum stress-induced apoptosis by enhancing DR5 expression in human carcinoma cells. *J Biol Chem* 2004;279:45495-45502.

98. Puthalakath H, O'Reilly LA, Gunn P, Lee L, Kelly PN, Huntington ND, et al. ER stress triggers apoptosis by activating BH3-only protein bim. *Cell* 2007;129:1337-1349.

99. Song B, Scheuner D, Ron D, Pennathur S, Kaufman RJ. Chop deletion reduces oxidative stress, improves beta cell function, and promotes cell survival in multiple mouse models of diabetes. *J Clin Invest* 2008;118:3378-3389.

100. Tsukano H, Gotoh T, Endo M, Miyata K, Tazume H, Kadomatsu T, et al. The endoplasmic reticulum stress-C/EBP homologous protein pathway-mediated apoptosis in macrophages contributes to the instability of atherosclerotic plaques. *Arterioscler Thromb Vasc Biol* 2010;30:1925-1932.

101. Fu HY, Okada K, Liao Y, Tsukamoto O, Isomura T, Asai M, et al. Ablation of C/EBP homologous protein attenuates endoplasmic reticulum-mediated apoptosis and cardiac dysfunction induced by pressure overload. *Circulation* 2010;122:361-369.

102. Namba T, Tanaka K, Ito Y, Ishihara T, Hoshino T, Gotoh T, et al. Positive role of CCAAT/enhancer-binding protein homologous protein, a transcription factor involved in the endoplasmic reticulum stress response in the development of colitis. *Am J Pathol* 2009;174:1786-1798.

103. Silva RM, Ries V, Oo TF, Yarygina O, Jackson-Lewis V, Ryu EJ, et al. CHOP/GADD153 is a mediator of apoptotic death in substantia nigra dopamine neurons in an in vivo neurotoxin model of parkinsonism. *J Neurochem* 2005;95:974-986.

104. Saxena S, Cabuy E, Caroni P. A role for motoneuron subtype-selective ER stress in disease manifestations of FALS mice. *Nat Neurosci* 2009;12:627-636.

105. Zhang K, Kaufman RJ. Signaling the unfolded protein response from the endoplasmic reticulum. *J Biol Chem* 2004;279:25935-25938.

106. Zhou Z, Licklider LJ, Gygi SP, Reed R. Comprehensive proteomic analysis of the human spliceosome. *Nature* 2002;419:182-185.

107. Liochev SI, Fridovich I. Superoxide and iron: partners in crime. *IUBMB Life* 1999;48:157-161.

108. Raha S, Robinson BH. Mitochondria, oxygen free radicals, disease and ageing. *Trends Biochem Sci* 2000;25:502-508.

109. Benson AM, Batzinger RP, Ou SY, Bueding E, Cha YN, Talalay P. Elevation of hepatic glutathione S-transferase activities and protection against mutagenic metabolites of benzo(a)pyrene by dietary antioxidants. *Cancer Res* 1978;38:4486-4495.

110. Benson AM, Hunkeler MJ, Talalay P. Increase of NAD(P)H:quinone reductase by dietary antioxidants: possible role in protection against carcinogenesis and toxicity. *Proc Natl Acad Sci U S A* 1980;77:5216-5220.

111. O'Brien PJ. Glycosylation of rhodopsin. *Methods Enzymol* 1982;81:783-788.

112. Benson AM, Cha YN, Bueding E, Heine HS, Talalay P. Elevation of extrahepatic glutathione S-transferase

and epoxide hydratase activities by 2(3)-tert-butyl-4-hydroxyanisole. *Cancer Res* 1979;39:2971-2977.

113. Meister A. New aspects of glutathione biochemistry and transport-selective alteration of glutathione metabolism. *Nutr Rev* 1984;42:397-410.

114. Alam J, Camhi S, Choi AM. Identification of a second region upstream of the mouse heme oxygenase-1 gene that functions as a basal level and inducer-dependent transcription enhancer. *J Biol Chem* 1995;270:11977-11984.

115. Primiano T, Kensler TW, Kuppusamy P, Zweier JL, Sutter TR. Induction of hepatic heme oxygenase-1 and ferritin in rats by cancer chemopreventive dithiolethiones. *Carcinogenesis* 1996;17:2291-2296.

116. Primiano T, Li Y, Kensler TW, Trush MA, Sutter TR. Identification of dithiolethione-inducible gene-1 as a leukotriene B4 12-hydroxydehydrogenase: implications for chemoprevention. *Carcinogenesis* 1998;19:999-1005.

117. Rushmore TH, Morton MR, Pickett CB. The antioxidant responsive element. Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. *J Biol Chem* 1991;266:11632-11639.

118. Rushmore TH, King RG, Paulson KE, Pickett CB. Regulation of glutathione S-transferase Ya subunit gene expression: identification of a unique xenobiotic-responsive element controlling inducible expression by planar aromatic compounds. *Proc Natl Acad Sci U S A* 1990;87:3826-3830.

119. Chanas SA, Jiang Q, McMahon M, McWalter GK, McLellan LI, Elcombe CR, et al. Loss of the Nrf2 transcription factor causes a marked reduction in constitutive and inducible expression of the glutathione S-transferase Gsta1, Gsta2, Gstm1, Gstm2, Gstm3 and Gstm4 genes in the livers of male and female mice. *Biochem J* 2002;365:405-416.

120. Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, et al. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochem Biophys Res Commun* 1997;236:313-322.

121. Ramos-Gomez M, Kwak MK, Dolan PM, Itoh K, Yamamoto M, Talalay P, et al. Sensitivity to carcinogenesis is increased and chemoprotective efficacy of enzyme inducers is lost in nrf2 transcription factor-deficient mice. *Proc Natl Acad Sci U S A* 2001;98:3410-3415.

122. Morimitsu Y, Nakagawa Y, Hayashi K, Fujii H, Kumagai T, Nakamura Y, et al. A sulforaphane analogue that potently activates the Nrf2-dependent detoxification pathway. *J Biol Chem* 2002;277:3456-3463.

123. Thimmulappa RK, Mai KH, Srisuma S, Kensler TW, Yamamoto M, Biswal S. Identification of Nrf2-regulated genes induced by the chemopreventive agent sulforaphane by oligonucleotide microarray. *Cancer Res* 2002;62:5196-5203.

124. Cullinan SB, Diehl JA. PERK-dependent activation of Nrf2 contributes to redox homeostasis and cell survival following endoplasmic reticulum stress. *J Biol Chem* 2004;279:20108-20117.

125. Punzo C, Xiong W, Cepko CL. Loss of daylight vision in retinal degeneration: are oxidative stress and metabolic dysregulation to blame? *J Biol Chem* 2012;287:1642-1648.

126. Szegezdi E, Fitzgerald U, Samali A. Caspase-12 and ER-stress-mediated apoptosis: the story so far. *Ann N Y Acad Sci* 2003;1010:186-194.

127. Van de Craen M, Vandenabeele P, Declercq W, Van den Brande I, Van Loo G, Molemans F, et al. Characterization of seven murine caspase family members. *FEBS Lett* 1997;403:61-69.

128. Morishima N, Nakanishi K, Takenouchi H, Shibata T, Yasuhiko Y. An endoplasmic reticulum stress-specific caspase cascade in apoptosis. Cytochrome c-independent activation of caspase-9 by caspase-12. *J Biol Chem* 2002;277:34287-34294.

129. Fischer H, Koenig U, Eckhart L, Tschachler E. Human caspase 12 has acquired deleterious mutations. *Biochem Biophys Res Commun* 2002;293:722-726.

130. Momoi T. Caspases involved in ER stress-mediated cell death. *J Chem Neuroanat* 2004;28:101-105.

131. Macario AJ, Conway De Macario E. Sick chaperones, cellular stress, and disease. *N Engl J Med* 2005;353:1489-1501.

132. Lindholm D, Wootz H, Korhonen L. ER stress and neurodegenerative diseases. *Cell Death Differ* 2006;13:385-392.

133. Bence NF, Sampat RM, Kopito RR. Impairment of the ubiquitin-proteasome system by protein aggregation. *Science* 2001;292:1552-1555.

134. Nishitoh H, Kadowaki H, Nagai A, Maruyama T, Yokota T, Fukutomi H, et al. ALS-linked mutant SOD1 induces ER stress- and ASK1-dependent motor neuron death by targeting Derlin-1. *Genes Dev* 2008;22:1451-1464.

135. Unterberger U, Höftberger R, Gelpi E, Flicker H, Budka H, Voigtländer T. Endoplasmic reticulum stress features are prominent in Alzheimer disease but not in prion diseases in vivo. *J Neuropathol Exp Neurol* 2006;65:348-357.

136. Katayama T, Imaizumi K, Sato N, Miyoshi K, Kudo T, Hitomi J, et al. Presenilin-1 mutations downregulate the signalling pathway of the

unfolded-protein response. *Nat Cell Biol* 1999;1:479-485.

137. Terro F, Czech C, Esclaire F, Elyaman W, Yardin C, Baclet MC, et al. Neurons overexpressing mutant presenilin-1 are more sensitive to apoptosis induced by endoplasmic reticulum-Golgi stress. *J Neurosci Res* 2002;69:530-539.

138. Milhavet O, Martindale JL, Camandola S, Chan SL, Gary DS, Cheng A, et al. Involvement of Gadd153 in the pathogenic action of presenilin-1 mutations. *J Neurochem* 2002;83:673-681.

139. Dawson TM, Dawson VL. Rare genetic mutations shed light on the pathogenesis of Parkinson disease. *J Clin Invest* 2003;111:145-151.

140. Takahashi R, Imai Y, Hattori N, Mizuno Y. Parkin and endoplasmic reticulum stress. *Ann N Y Acad Sci* 2003;991:101-106.

141. Imai Y, Soda M, Takahashi R. Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity. *J Biol Chem* 2000;275:35661-35664.

142. Petrucelli L, O'Farrell C, Lockhart PJ, Baptista M, Kehoe K, Vink L, et al. Parkin protects against the toxicity associated with mutant alpha-synuclein: proteasome dysfunction selectively affects catecholaminergic neurons. *Neuron* 2002;36:1007-1019.

143. Paulson HL, Bonini NM, Roth KA. Polyglutamine disease and neuronal cell death. *Proc Natl Acad Sci U S A* 2000;97:12957-12958.

144. Kouroku Y, Fujita E, Jimbo A, Kikuchi T, Yamagata T, Momoi MY, et al. Polyglutamine aggregates stimulate ER stress signals and caspase-12 activation. *Hum Mol Genet* 2002;11:1505-1515.

145. Harjes P, Wanker EE. The hunt for huntingtin function: interaction partners tell many different stories. *Trends Biochem Sci* 2003;28:425-433.

146. Gervais FG, Singaraja R, Xanthoudakis S, Gutekunst CA, Leavitt BR, Metzler M, et al. Recruitment and activation of caspase-8 by the Huntingtin-interacting protein Hip-1 and a novel partner Hippi. *Nat Cell Biol* 2002;4:95-105.

147. Ybe JA, Mishra S, Helms S, Nix J. Crystal Structure at 2.8 A of the DLLRKN-containing coiled-coil domain of huntingtin-interacting protein 1 (HIP1) reveals a surface suitable for clathrin light chain binding. *J Mol Biol* 2007;367:8-15.

148. Kovacs GG, Budka H. Prion diseases: from protein to cell pathology. *Am J Pathol* 2008;172:555-565.

149. Kondo S, Saito A, Hino SI, Murakami T, Ogata M, Kanemoto S, et al. BBF2H7, a novel transmembrane bZIP transcription factor, is a new type of endoplasmic reticulum stress transducer. *Mol Cell Biol* 2007;27:1716-1729.

150. DuRose JB, Tam AB, Niwa M. Intrinsic capacities of molecular sensors of the unfolded protein response to sense alternate forms of endoplasmic reticulum stress. *Mol Biol Cell* 2006;17:3095-3107.

151. Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. *J Clin Invest* 2005;115:2656-2664.

152. Rutkowski DT, Arnold SM, Miller CN, Wu J, Li J, Gunnison KM, et al. Adaptation to ER stress is mediated by differential stabilities of pro-survival and pro-apoptotic mRNAs and proteins. *PLoS Biol* 2006;4:e374.

153. Surguchev A, Surguchov A. Conformational diseases: looking into the eyes. *Brain Res Bull* 2010;81:12-24.

154. Salminen A, Kauppinen A, Hyttinen JM, Toropainen E, Kaarniranta K. Endoplasmic reticulum stress in age-related macular degeneration: trigger for neovascularization. *Mol Med* 2010;16:535-542.

155. Jun AS, Meng H, Ramanan N, Matthaei M, Chakravarti S, Bonshek R, et al. An alpha 2 collagen VIII transgenic knock-in mouse model of Fuchs endothelial corneal dystrophy shows early endothelial cell unfolded protein response and apoptosis. *Hum Mol Genet* 2012;21:384-393.

156. Watson GW, Andley UP. Activation of the unfolded protein response by a cataract-associated αA-crystallin mutation. *Biochem Biophys Res Commun* 2010;401:192-196.

157. Firtina Z, Danysh BP, Bai X, Gould DB, Kobayashi T, Duncan MK. Abnormal expression of collagen IV in lens activates unfolded protein response resulting in cataract. *J Biol Chem* 2009;284:35872-35884.

158. Carbone MA, Chen Y, Hughes GA, Weinreb RN, Zabriskie NA, Zhang K, et al. Genes of the unfolded protein response pathway harbor risk alleles for primary open angle glaucoma. *PLoS* 2011;6:e20649.

159. Bonapace G, Waheed A, Shah GN, Sly WS. Chemical chaperones protect from effects of apoptosis-inducing mutation in carbonic anhydrase IV identified in retinitis pigmentosa 17. *Proc Natl Acad Sci U S A* 2004;101:12300-12305.

160. Datta R, Waheed A, Bonapace G, Shah GN, Sly WS. Pathogenesis of retinitis pigmentosa associated with apoptosis-inducing mutations in carbonic anhydrase IV. *Proc Natl Acad Sci U S A* 2009;106:3437-3442.

161. Rebello G, Ramesar R, Vorster A, Roberts L, Ehrenreich L, Oppon E, et al. Apoptosis-inducing signal sequence mutation in carbonic anhydrase IV identified in patients with the RP17 form of retinitis pigmentosa. *Proc Natl Acad Sci U S A* 2004;101:6617-6622.

162. Kanekura K, Suzuki H, Aiso S, Matsuoka M. ER stress and unfolded protein response in amyotrophic lateral sclerosis. *Mol Neurobiol* 2009;39:81-89.

163. Matus S, Glimcher LH, Hetz C. Protein folding stress in neurodegenerative diseases: a glimpse into the ER. *Curr Opin Cell Biol* 2011;23:239-252.

164. Gorbatyuk MS, Knox T, LaVail MM, Gorbatyuk OS, Noorwez SM, Hauswirth WW, et al. Restoration of visual function in P23H rhodopsin transgenic rats by gene delivery of BiP/Grp78. *Proc Natl Acad Sci U S A* 2010;107:5961-5966.

165. Kang MJ, Ryoo HD. Suppression of retinal degeneration in Drosophila by stimulation of ER-associated degradation. *Proc Natl Acad Sci U S A* 2009;106:17043-17048.

166. Mendes CS, Levet C, Chatelain G, Dourlen P, Fouillet A, Dichtel-Danjoy ML, et al. ER stress protects from retinal degeneration. *EMBO J* 2009;28:1296-1307.

167. Vogel M, Mayer MP, Bukau B. Allosteric regulation of Hsp70 chaperones involves a conserved interdomain linker. *J Biol Chem* 2006;281:38705-38711.

168. Ethen CM, Reilly C, Feng X, Olsen TW, Ferrington DA. The proteome of central and peripheral retina with progression of age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2006;47:2280-2290.

169. Tuo J, Bojanowski CM, Zhou M, Shen D, Ross RJ, Rosenberg KL, et al. Murine ccl2/cx3cr1 deficiency results in retinal lesions mimicking human age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2007;48:3827-3836.

170. Cohen FE, Kelly JW. Therapeutic approaches to protein-misfolding diseases. *Nature* 2003;426:905-909.

171. Chaudhuri TK, Paul S. Protein-misfolding diseases and chaperone-based therapeutic approaches. *FEBS J* 2006;273:1331-1349.

172. Bernier V, Lagacé M, Bichet DG, Bouvier M. Pharmacological chaperones: potential treatment for conformational diseases. *Trends Endocrinol Metab* 2004;15:222-228.

173. Papp E, Csermely P. Chemical chaperones: mechanisms of action and potential use. *Handb Exp Pharmacol* 2006;172:405-416.

174. Shin SH, Murray GJ, Kluepfel-Stahl S, Cooney AM, Quirk JM, Schiffmann R, et al. Screening for pharmacological chaperones in Fabry disease. *Biochem Biophys Res Commun* 2007;359:168-173.

175. Figler RA, Omote H, Nakamoto RK, Al-Shawi MK. Use of chemical chaperones in the yeast Saccharomyces cerevisiae to enhance heterologous membrane protein expression: high-yield expression and purification of human P-glycoprotein. *Arch Biochem Biophys* 2000;376:34-46.

176. Skach WR. Pharmacological chaperoning: two 'hits' are better than one. *Biochem J* 2007;406:e1-2.

177. Lai E, Teodoro T, Volchuk A. Endoplasmic reticulum stress: signaling the unfolded protein response. *Physiology (Bethesda)* 2007;22:193-201.

178. Liu CY, Wong HN, Schauerte JA, Kaufman RJ. The protein kinase/endoribonuclease IRE1alpha that signals the unfolded protein response has a luminal N-terminal ligand-independent dimerization domain. *J Biol Chem* 2002;277:18346-18356.

179. Illing ME, Rajan RS, Bence NF, Kopito RR. A rhodopsin mutant linked to autosomal dominant retinitis pigmentosa is prone to aggregate and interacts with the ubiquitin proteasome system. *J Biol Chem* 2002;277:34150-34160.

180. Noorwez SM, Kuksa V, Imanishi Y, Zhu L, Filipek S, Palczewski K, et al. Pharmacological chaperone-mediated in vivo folding and stabilization of the P23H-opsin mutant associated with autosomal dominant retinitis pigmentosa. *J Biol Chem* 2003;278:14442-14450.

181. Noorwez SM, Malhotra R, McDowell JH, Smith KA, Krebs MP, Kaushal S. Retinoids assist the cellular folding of the autosomal dominant retinitis pigmentosa opsin mutant P23H. *J Biol Chem* 2004;279:16278-16284.

182. Surgucheva I, Ninkina N, Buchman VL, Grasing K, Surguchov A. Protein aggregation in retinal cells and approaches to cell protection. *Cell Mol Neurobiol* 2005;25:1051-1066.

183. Balch WE, Morimoto RI, Dillin A, Kelly JW. Adapting proteostasis for disease intervention. *Science* 2008;319:916-919.

184. Perlmutter DH. Chemical chaperones: a pharmacological strategy for disorders of protein folding and trafficking. *Pediatr Res* 2002;52:832-836.

185. Erbay E, Babaev VR, Mayers JR, Makowski L, Charles KN, Snitow ME, et al. Reducing endoplasmic reticulum stress through a macrophage lipid chaperone alleviates atherosclerosis. *Nat Med* 2009;15:1383-1391.

186. Ozcan L, Ergin AS, Lu A, Chung J, Sarkar S, Nie D, et al. Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metab* 2009;9:35-51.

187. Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* 2006;313:1137-1140.