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REVIEW ARTICLE

# Role of Endoplasmic Reticulum Stress and Unfolded Protein Responses in Health and Diseases

**Abbas Ali Mahdi**[1] · **Syed Husain Mustafa Rizvi**[1] · **Arshiya Parveen**[1]

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**Abstract** Endoplasmic reticulum (ER) is the site of protein synthesis, protein folding, maintainance of calcium homeostasis, synthesis of lipids and sterols. Genetic or environmental insults can alter its function generating ER stress. ER senses stress mainly by three stress sensor pathways, namely protein kinase R-like endoplasmic reticulum kinase-eukaryotic translation-initiation factor 2α, inositol-requiring enzyme 1α-X-box-binding protein 1 and activating transcription factor 6-CREBH, which induce unfolded protein responses (UPR) after the recognition of stress. Recent studies have demonstrated that ER stress and UPR signaling are involved in cancer, metabolic disorders, inflammatory diseases, osteoporosis and neurodegenerative diseases. However, the precise knowledge regarding involvement of ER stress in different disease processes is still debatable. Here we discuss the possible role of ER stress in various disorders on the basis of existing literature. An attempt has also been made to highlight the present knowledge of this field which may help to elucidate and conjure basic mechanisms and novel insights into disease processes which could assist in devising better future diagnostic and therapeutic strategies.

**Keywords** ER stress · UPR · Diseases · Chaperons

✉ Abbas Ali Mahdi
biochemistrykgmu@gmail.com; abbasalimahdi@gmail.com

[1] Department of Biochemistry, King George's Medical University, Lucknow 226003, Uttar Pradesh, India

## Introduction

Recent developments highlighting new insights into the endoplasmic reticulum (ER) stress regulated pathways, and their role in various diseases, have attracted immense attention towards this organelle. ER is a multifunctional organelle coordinating numerous functions fundamental for cell survival. It is the site of protein synthesis, protein folding, synthesis of lipids and sterols, maintenance of calcium homeostasis and post translational modifications of proteins [1–3]. Genetic or environmental insults can alter the functions of ER through calcium imbalance, redox imbalance, glucose starvation, altered glycosylation of glycoproteins and protein misfolding, each of which can induce ER stress [1–4]. In other words ER stress can be pictured as perturbation arising from failure in execution of functions assigned to ER or hindered working capacity of this organelle. To escape such adverse conditions, ER activates stress sensor pathway termed as unfolded protein response (UPR) through complex signaling network of Protein kinase R-like endoplasmic reticulum kinase-eukaryotic translation-initiation factor 2α (PERK-eIF2α), inositol-requiring enzyme 1α-X-box-binding protein 1 (IRE1-XBP1), activating transcription factor 6-CREBH (ATF6-CREBH) transducers. This signaling network initiates changes in the expression of hundreds of genes to restore cellular homeostasis. For instance, halting of the global protein synthesis, through general translation arrest, elevates the expression of ER chaperons which enhances protein folding so as to maintain the quality control of proteins while the misfolded proteins get degraded through the ER-associated degradation (ERAD) and autophagy. However, if the ER stress is prolonged, then UPR activates apoptotic signaling which may progress through mitochondrial dependent or independent pathways [Reviews; 5–8].

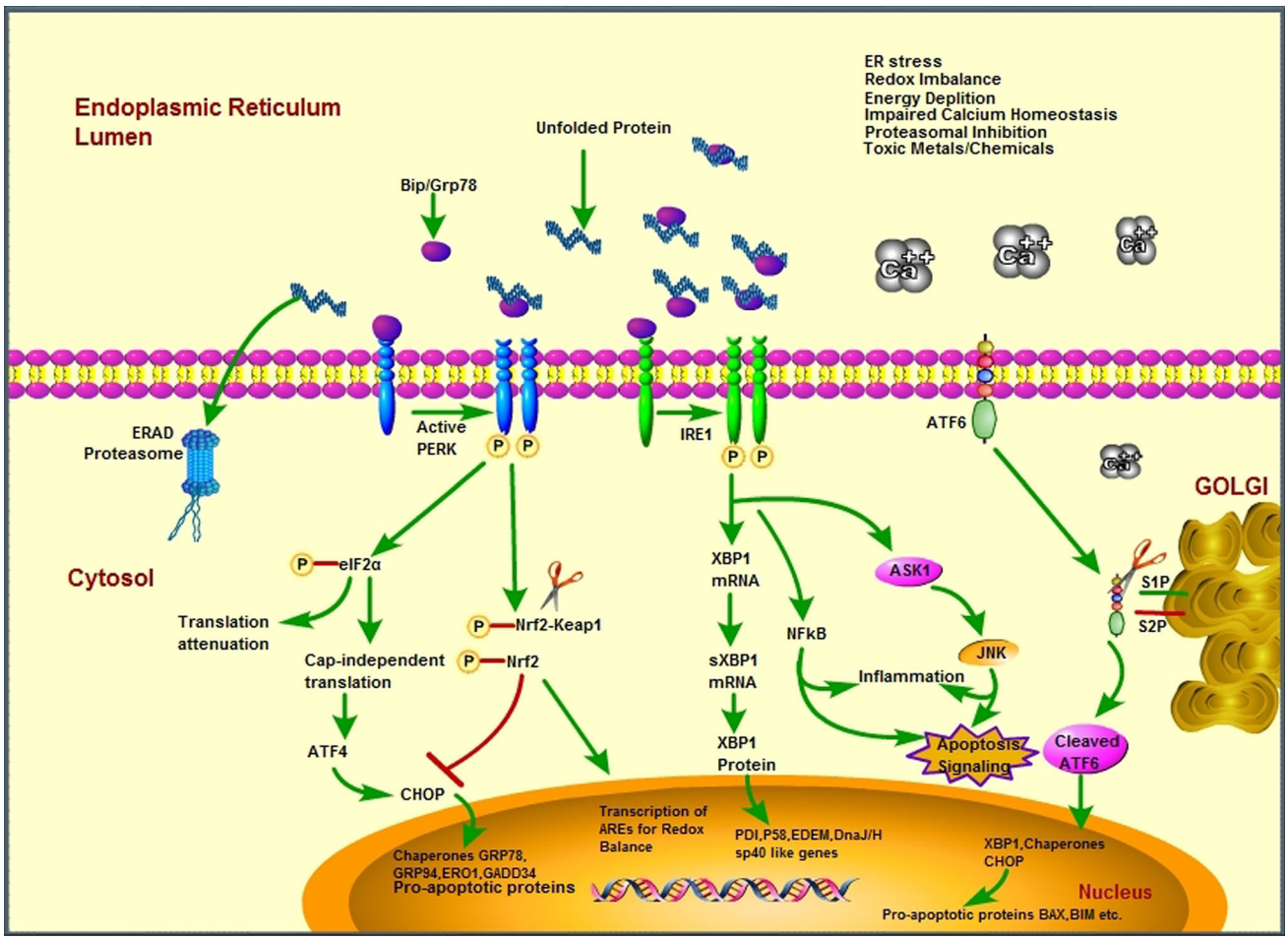


**Fig. 1** Scheme illustrating the interplay between different signaling pathways induced in an event of unfolded protein response and subsequent endoplasmic reticulum dysfunction in human diseases

ER senses stress mainly by three stress sensors namely Protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1) and activating transcription factor 6 (ATF6). These sensors induce UPR after the recognition of ER stress/misfolding of proteins. During normalcy, ER-luminal domains of UPR transducers like IRE1, PERK and ATF6 are associated with the glucose-regulated protein 78 (Bip/Grp 78), an HSP 70 family protein. Bip/Grp 78 maintains the homeostasis of these signaling transducers. When ER is subjected to stress, Bip/Grp78 is sequestered by unfolded proteins in ER, resulting in its dissociation from the UPR transducers and hence activation of these molecules [2, 9–11] see Fig. 1.

## ER Stress and Apoptotic Signaling

Apoptosis, while on one hand, is fundamental to normal development and maintenance of tissue homeostasis, on the other, it is also a process by which physiologically normal cells may die under stress or unfavorable conditions. Apoptosis is implicated in several human diseases like diabetes, hepatic disorders, neurodegenerative disorders like Alzheimer's and Parkinsons disease etc. Prolonged ER stress result into the activation of apoptotic signaling through UPR [12, 13]. During ER stress, calcium ($Ca^{++}$) effluxes from the ER increase cytosolic $Ca^{++}$ levels and disturb the mitochondrial membrane potential [14], which results into the release of cytochrome c and forms apoptosome complex with Apaf1 and caspase 9. This complex further activates the executioner caspases like caspase 3 and caspase 7 which leads to apoptosis [15–17]. ER membrane associated caspase 12 is also implicated in the activation of apoptosis through direct activation of caspase 3 or by caspase 9. CHOP/GADD153, sensor of endoplasmic reticulum stress, is highly up-regulated during ER stress [18, 19]. In our studies, caspase 12 activation was observed to be associated with enhanced intracellular calcium levels together with increased mRNA and protein levels of CHOP/GADD153 [20, 21]. CHOP is known to inhibit the expression of antiapoptotic $Bcl_2$ family proteins and disturbs the ratio of Bax/$Bcl_2$ [22, 23]. Several lines of

evidences suggest that $Bcl_2$ family member proteins are localized in both mitochondria and ER [24]. Whenever these organelles sense stress, the ratio of pro- and anti-apoptotic proteins gets disturbed which leads to initiation of apoptotic signaling. Furthermore, CHOP activates GADD34, which interacts with the phosphatase 1 and dephosphorylates eIf2α which results into the protein overload in ER [25–27]. IRE1α, an arm of UPR, induces apoptosis in ER stress through its association with TNF-receptor associated factor 2 (TRAF2) which activates caspase 12 and apoptosis signal regulating kinase 1 (ASK1) which in turn activates the pro-apoptotic signaling through c- Jun N-terminal kinase (JNK) [28, 29]. Disturbed apoptotic signaling is associated in various human diseases and the above reports clearly implicate the involvement of ER stress and UPR signaling in apoptosis.

## ER Stress and Oxidative Stress

Reactive free radicals, including both reactive oxygen species (ROS) and reactive nitrogen species (RNS), could be substantially produced in response to multiple stresses, in different cellular sub compartments [30–32]. ER provides an exclusive oxidizing environment to the proteins to facilitate disulfide bond formation [33–35], and the ROS generated as a result of this process in ER alone contributes to 25 % of ROS generated by the cell [36]. Two enzymatic components, protein disulfide isomerase (PDI) and endoplasmic reticulum oxidoreductin (ERO-1) are often implicated in promoting oxidative stress in the ER compartment of the cell. PDI catalyzes disulfide bond formation between thiol moieties through thiol-disulfide oxidation, reduction, and isomerization. PDI which is itself reduced in the process is oxidized by ERO-1 via transfer of electrons from reduced PDI to molecular oxygen ($O_2$) resulting in oxidative stress [37]. This may imply that oxidation of multiple disulfide bonds would generate high levels of cellular ROS. Further, any erroneous disulfide bonds so generated in the process are subsequently reduced by glutathione (GSH). This further diminishes the reduced glutathione pool altering the redox environment within the ER.

There are also evidences which suggest that ROS may be generated when accumulation of unfolded proteins in the ER elicits $Ca^{2+}$ leakage into the cytosol through inositol trisphosphate receptor (IP3R) [36, 38]. The perturbed cytoplasmic calcium levels evoke influx of $Ca^{2+}$ in the nuclei and mitochondria [39] resulting in generation of ROS. Since protein folding and refolding in the ER lumen are highly energy-dependent processes, ATP depletion consequential to protein misfolding may stimulate mitochondrial oxidative phosphorylation to increase ATP and ROS production. In addition, ER transmembrane protein NADPH oxidase complex, Nox4 may also be involved in producing superoxide anion and hydrogen peroxide [40].

Cellular oxidative stress leads to activation of antioxidant defense genes which are orchestrated mainly by the Nrf bZIP-family of transcription factors [20, 41, 42]. There are reports indicating possible relationship between Nrf bZIP-family proteins and ER stress defenses. Nrf1 and Nrf3 proteins of this family have been reported to be associated with the ER membrane and nuclear envelope which suggest their involvement in ER- related functions [43, 44]. A study in *Caenorhabditis elegans* [45] revealed that SKN-1, the Nrf ortholog, plays a critical role in resistance to oxidative and ER stress. Moreover, it has been reported that the response mobilized by SKN-1/Nrf under UPR is observed to be overlapping but still distinct from that evoked during oxidative stress conditions [45]. SKN-1/Nrf is reported to be activated by ER stress, independent of ROS signaling, and it provides resistance against reductive stress as well [45]. Furthermore, studies also report that PERK activates nuclear respiratory factor 2 (Nrf2) [17]. Nrf2 in turn regulates the protective mechanism within the cells against oxidative stress by the transcription of antioxidant enzymes. In unstressed cells Nrf2 resides in the cytoplasm, through its association with the kelch-like Ech-associated protein 1(Keap1), however, stress induces the dissociation of Nrf2 from keap1, enabling its nuclear translocation and activation. PERK is also known to phosphorylate Nrf2 [46, 47], during ER stress, leading to its nuclear accumulation, where it binds to the antioxidant response element (ARE) and induces transcription of antioxidant enzymes like heam oxygenase1 and glutathione S-transferase etc. [17] see Fig. 1. Hence, ER signaling has a broader impact on cellular stress defense networks that are critical in coordination of ER and cytoplasmic homeostasis.

## ER Stress and Inflammatory Responses

ER stress and inflammatory responses are implicated in the pathogenesis of various diseases including neurodegenerative, respiratory, cardiovascular, cancer, diabetes and other metabolic diseases [48–51]. UPR signaling evokes inflammatory reactions, through three arms of UPR, that are PERK, IRE1 and ATF6, which in turn induce the activation of NF-κB [52, 53]. NF-κB generally resides in the cytoplasm, in inactive form through its association with IkB protein, which prevents its activation and nuclear translocation. Acute or chronic stress results into the activation of NF-κB by the proteosome based degradation of IkB. Studies have revealed that IRE1α degrades IkB and causes activation and nuclear translocation of NF-κB, while PERK activates NF-κB through translational

suppression of IkB. Moreover, IRE1 activates AP1, a transcription factor that can induce the expression of tumor necrosis factor (TNF), keratinocyte growth factor (KGF), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-8, and certain cytokine receptors [54–56]. Furthermore, UPR via ATF6 [52, 53] has been implicated in the activation of acute phase response (APR), which is generated immediately after tissue damage, infection and inflammation etc. Acute phase proteins (APPs) concentration increases in serum after the onset of above conditions, ultimately causing fever, neurological and pathological changes.

NLRP3 inflammasome has recently been recognized as an innate immune signaling receptor that plays key role in mediating cell responses to various endo- and exogenous signals. Recent reports indicate that inflammasomes play a critical role in a number of autoimmune and metabolic diseases. NF-κB activates pro-IL1β which is converted to mature IL1β by the NLRP3, ASC and caspase 1 complex [57, 58]. Moreover, ROS and lysosomal damage also activates NALP3 inflammasome pathway and induce pro-inflammatory reactions. Reports clearly indicate that ER stress induces pro IL1β and NLRP3 inflammasome activation [59, 60] through NF-κB pathway. The findings thus surmise the role of ER stress in inflammatory pathways and its related diseases.

## ER Stress and Osteoporosis

Osteoporosis is a major health problem in ageing population. It is characterized by reduced bone strength due to which susceptibility of fractures is common. Low bone mineral density (BMD) which is the hallmark of osteoporosis, has been related to ER stress. PERK-eIf2α signaling is required for normal development of the postnatal growth, function and viability of pancreas and skeletal system [61, 62]. A study by Jie Liu et al. showed that low BMD haplotype is distinct, due to associated single nucleotide polymorphism, which is exhibited by increased phosphorylation of eIF2α during ER stress, as compared to alternate haplotype [63]. The balance between osteoblasts (the mesenchymal stem cells derived bone forming cells) and osteoclasts (the hematopoietic stem cells derived bone resorption cells) is very important for the normal functioning and development of bone [64–66]. He et al. reported that blocking of dephosphorylation of eIf2α by Salubrinal increases the osteoblast differentiation. They also hypothesized that ER-stress regulation through eIF2α and ATF4 could be a good system for antiosteoporosis [67]. Diabetic patients are more prone to fractures especially that of hip and upper extremities as compared with the non-diabetics [68]. Insulinopenia and hyperglycemia cause low BMD which impairs bone formation [69]. Moreover, it is reported that diabetes itself induces expression of ER stress specific CHOP in osteoblast cells resulting in the progression of apoptosis in these cells [70]. Therefore, the balance between the osteoblasts and osteoclasts are disturbed which leads to the bone disorders and development of diabetic osteoporosis [70]. IRE1α-XBP1 pathways are crucial for osteoblast maturation and play important role in bone formation and bone resorption under pathological conditions [71]. Furthermore, there are reports that ER specific molecular chaperones like BiP (immunoglobulin heavy-chain binding protein) and PDI (protein-disulfide isomerase) are down-regulated in osteoblasts obtained from osteoporosis patients [72]. These findings suggest the importance of ER stress in osteoporosis, skeletal development and also for devising therapeutic strategies against skeletal diseases.

## ER Stress and Cancer

There are reports that cancer cells require high protein folding capacity of ER chaperons due to their enhanced rate of growth and proliferation. The characteristics of tumor microenvironment like hypoxia, redox imbalance, pH fluctuations and nutrient starvation are the inducers of UPR [73]. Moreover, it has been reported that UPR signaling is upregulated in cancer cells [8]. It is also reported that the redox imbalance due to hypoxic condition in cancer cells results in the activation of UPR pathway. Studies have also shown that Grp78 is highly expressed in prostate, lung, breast and colon cancers [74–81]. Furthermore, a study showed that cells which do not expresse Grp78 are unable to form tumor [82]. The above studies validate the importance of Grp78 chaperon in tumor formation. In essence, Grp78 increases the protein folding capacity of ER thus reducing stress evoked cell death in cancer cells. The PERK arm of the UPR also plays important role in tumor proliferation and survival. Inactivation of the PERK pathway by either generating mutations in the kinase domain of PERK or introducing a phosphorylation-resistant form of eIF2α impairs cell survival under extreme hypoxia [83]. Furthermore, PERK limits oxidative DNA damage through Nrf2 activation which further promotes cancer cell proliferation and survival [84]. The involvement of UPR in cancer is currently promising therapeutic target for the treatment of cancer [85].

Tumor suppressor gene TP53, which is activated during different stressful conditions, plays pivotal role in several biological mechanisms including promotion of cell cycle arrest, senescence and apoptosis, [86–90]. TP53 regulation in ER stress is debatable. Studies have revealed that ER

stress stabilizes p53 activity and induces p53 mediated apoptosis. On the other end, reports also showed that ER stress induced downregulation of p53 by Gsk3β [91, 92]. In a report from our lab downregulation of p53 was observed in response to aluminium mediated ER stress in SHSY-5Y cells [20]. Moreover, in a clinical setting, tumorigenesis as well as the efficacy of therapy may be influenced by the ability of ER stress to inhibit p53. This would confer resistance to the inhibitory effect of ER stress on p53 functionality and may prove disastrous to tumors that retain wild type p53 gene. Such an effect would enable the cancerous cells to resist DNA damaging effect of agents used in cancer treatment. In such an event, inhibiting ER stress may serve as a useful strategy to augment the efficacy of therapy directed against cancer progression.

## ER Stress and Neurodegeneration

Causes of neurodegenerative disorders are multi-factorial including redox imbalance, environmental factors, genetic predisposition, glutamate-induced excitotoxicity, neuroinflammation, disruption in $Ca^{2+}$ levels, mitochondrial dysfunction and misfolded protein accumulation. In this section of the review we have focused on the relationship between ER stress in terms of UPR activation and its role in neurodegenerative diseases. Accumulation of misfolded proteins is a distinguishing aspect of many neurodegenerative diseases including Alzheimer's [93] and Parkinson's disease [94]. As discussed above accumulation of misfolded proteins causes ER stress and activates UPR. Here we discuss the role of UPR in two major neurodegenerative diseases, i.e. AD and PD.

## ER Stress and Alzheimer's Disease

Alzheimer's disease is characterized by the deposition of toxic senile plaques of β amyloid protein and intracellular neurofibrillary tangles containing hyperphosphorylated tau [95]. The β amyloid proteins are formed as a result of cleavage of amyloid precursor protein (APP) by the action of β-secretase (BACE) and ϒ-secretase. ER stress sensors IRE1 and PERK are greatly influenced by presenilin protein, which is an integral membrane protein and a part of the ϒ-secretase complex, and is widely expressed in both ER and Golgi apparatus [96]. Reports indicate that mutated presenilin reduces the phosphorylation of PERK-eIF2α pathway which results in the accumulation of proteins in ER [97]. Moreover, studies report increased PERK and eIF2α levels in hippocampus neurons of AD brain [98, 99]. These observations necessitate further experimentation to carefully dissect the PERK-eIF2α pathway in AD. Furthermore, mutant presenilin 1 inhibits IRE1 signalling, which in turn stalls or suppresses the transcription of ER chaperones such as GRP78, which has been reported to be down-regulated in AD [97]. XBP1, also implicated in AD, is known to control diverse cell type- and context-dependent transcriptional regulatory networks [100]. Modulation of IRE1 activity can reduce or delay splicing of XBP1, thus switching signalling to a pro-death response [101].

Generation of Aβ, a characteristics hallmark of AD, is also associated with ER [102, 103]. Aβ is reported to induce $Ca^{2+}$ release from ER stores [104]. However, reports also suggest that influx of $Ca^{2+}$, through calcium channels located on plasma membrane or ER membrane, increases Aβ generation [105] by alteration in the metabolism and production of Aβ. Whatsoever may be the cause there is no doubt that an intricate relationship exist between $Ca^{2+}$ dysfunction and AD [106]. Furthermore, $Ca^{2+}$ homeostasis is essential for the proper functioning of ER chaperons and protein folding. In our previous study we observed an association between increased intracellular calcium and Aβ(1–40) levels in neuronal cells apart from enhanced CHOP and caspase12 levels [20]. It may be stated that another characteristic feature of AD is tau pathology. Tau is a microtubule associated protein present in neurons which maintains microtubule assembly and stabilization. ER stress is normally linked with the early stages of tau pathology [107, 108]. Tau proteins become hyperphosphorylated in pathological conditions, which results in its dissociation from microtubule assembly into unusual toxic filaments [109]. The unfolded protein response activated in pretangle neurons in AD hippocampus has been shown to be closely associated with the presence of phosphorylated tau (p-tau) and GSK-3$\beta$ [98]. These findings elicit activation of UPR in AD neurons at an early stage of neurofibrillary degeneration. Moreover, prolonged activation of UPR may be involved in both tau phosphorylation and neurodegeneration in AD pathogenesis [110].

## ER Stress and Parkinson's Disease

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta along with the presence of intraneuronal cytoplasmic inclusion bodies, known as Lewy bodies in the neurons [111]. Most of the cases of PD, up to 90 %, are sporadic while only 5–10 % of patients show monogenic form of the disease [112]. Recent studies investigating implication of ER stress in the pathophysiology of PD have reported increased UPR activity in the affected brain regions of PD patients and also in patients suffering from the related multi-systems atrophy syndrome [113, 114]. It has been

reported by Silva et al. [115], that deficiency of CHOP, a key ER stress marker, protects the neonatal striatum from neurotoxicant 6-hydroxydopamine. Reports also showed that forced expression of ER stress sensor proteins, ATF6 alpha [117] and spliced XBP1 [116], confines neurotoxin-induced dopaminergic neuronal death [117]. These reports are indicative of the role of ER stress in the death and dysfunction of dopaminergic neurons exposed to neurotoxicant models of PD.

Accumulation of misfolded proteins like α-synuclein and Parkin-associated endothelin receptor-like receptor (Pael-R) has been reported to be a key event which triggers UPR in the ER. α-synuclein is an autosomal dominant PD gene expressed in synaptic vesicles and in nervous tissue. Post-translational modifications, like phosphorylation and nitrosylation, of α-synuclein can cause misfolding and later deposition of the protein into Lewy bodies in the substantia nigra of PD patients [118]. Smith et al. [119] reported that A53T mutation in α-synuclein activates UPR resulting in increased expression of CHOP and GRP78 and increased phosphorylation of eIF2 α. Furthermore, the authors also reported that suppressing UPR through inhibition of eIF2α phosphorylation protected the A53T mutant α-synuclein-overexpressing cells from cell death. These reports suggest that UPR mediates shift of the balance towards apoptosis [119]. Moreover, mutations in leucine-rich repeat kinase 2 (LRRK2), also an autosomal dominant PD gene, causes impairment in protein degradation pathways, accumulation of oxidized proteins, impairment of the autophagy-lysosomal pathway, accumulation of α-synuclein and ubiquitinated proteins [120]. LRRK2 has been observed to localize in core of Lewy bodies [121] and is known to upregulate GRP78, a key cell survival molecule during ER stress [122]. In addition to α-synuclein and LRRK2, Pael-R has also been detected to accumulate in the core of Lewy bodies in sporadic PD [123]. Parkin, an autosomal recessive PD gene, is an E3 ubiquitin ligase that plays an important role in protein degradation of the misfolded Pael-R [124]. Mutational loss of E3 activity of parkin has been observed to cause unfolded Pael-R to accumulate and finally induce ER stress mediated cell death [125].Therefore, ER stress generated in response to accumulation of unfolded Pael-R is suggested to be another pathophysiological mechanism underlying autosomal recessive PD [126–128].

The above findings discussed in relation to AD and PD illustrate the paramount significance of ER stress in development and progression of these diseases. Scientific literature similarly supports the involvement of ER stress in other neurodegenerative disorders like Amyotrophic lateral sclerosis, Huntington diseases and Prions disease etc. (see reviews Cláudia [110], Omura et al. [128], Lindholm et al. [5]).

## Conclusion

It may be concluded that ER plays a crucial role in protein synthesis and folding. UPR which forms the critical arm of ER stress signaling, gets activated in response to stress and times when ER stress is prolonged, UPR assumes adverse role, through disruption of cellular homeostasis. Overall the existing literature clearly indicates the role of ER stress in health and diseases (Table 1). Furthermore, dissection of

**Table 1** Role of UPR transducers and proteins in different human diseases

| Protein | Function | Disease | References |
|---|---|---|---|
| IRE1 | UPR sensor | Human somatic cancers; Alzheimer's disease; Parkinson's disease; ALS | [97, 129, 130, 131, 132] |
| CREBH | Regulate expression of PPARα, HNF4α, and ATF6 α | Extreme hypertriglyceridemia | [133, 134, 135] |
| ATF6α | UPR sensor | Type 2 diabetes and pre-diabetic traits; Increased plasma cholesterol levels; Alzheimer's disease; ALS | [97, 136, 137, 138, 139] |
| PERK | UPR sensor | Wolcott–Rallison syndrome; Alzheimer's disease; Wolcott–Rallison syndrome; supranuclear palsy; ALS | [5, 97, 98, 131, 140, 141, 142] |
| ATF4 | UPR sensor | Parkinson's disease | [143] |
| Grp78 (BiP) | Senses ER stress, accumulation of misfolded proteins and regulate expression of ATF6α and ATF4 | Bipolar disorder; Alzheimer's disease | [144, 145, 146, 147] |
| PPT1 | Palmitoylprotein thioesterase-1 | Batten disease/infantile neuronal ceroid lipofuscinosis | [148] |
| CHOP | Regulate expression of ATF4 and ATF6α | Early-onset type 2 diabetes in Italians | [116, 149, 150, 151, 152] |
| WFS1 | Regulate expression of XBP1 s | Wolfram syndrome; risk of type 2 diabetes in Japanese and European populations | [153, 154, 155, 156] |
| XBP1? | UPR sensor | Bipolar disease | [157, 158] |

? Denotes discrepancy in outcome of studies exploring the relation between XBP1 and bipolar disorder

ER stress signaling could unravel new avenues that may potentially be exploited for developing future therapeutics to address ER stress-related anomalies.

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**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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