Chapter

The Relationship of Some Neurodegenerative Diseases with Endoplasmic Reticulum Stress and Histopathological Changes in These Diseases: An Overview

Adem Kara, Volkan Gelen and Hülya Kara

Abstract

The endoplasmic reticulum (ER) is an organelle responsible for protein production in the cell and provides hemostasis in the cell. ER stress is stimulated by folded proteins, while the unfolded protein response (UPR) creates a response to ER stress and provides the cell survival. UPR modulation in mammals is provided with three major ER stress sensors, including transmembrane kinase 1, protein kinase-like ER kinase, and activating transcription factor 6. Because neurons are susceptible to misfolded proteins, severe or prolonged ER stress activates apoptotic cell death signals in the cell. Neurodegenerative diseases characterized by this condition are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, characterized by the accumulation and aggregation of misfolded proteins. In addition, ER stress can lead to depression, schizophrenia, sleep disruption, and post-traumatic stress disorders. Neurons are highly susceptible to protein misfolding and apoptotic cell death. For this reason, UPR modulation contributes to preventing the neurodegenerative process in cells with misfolded protein folding. The relationship between ER stress, UPR, and neuropathology is significant for understanding this process. This section will discuss the effects of ER stress between UPR modulation and neurodegenerative disorders, and the histopathological changes in the mentioned neurodegenerative diseases will be mentioned.

Keywords: ER stress, neurodegenerative disease, apoptosis, histopathology, neuropathology

1. Introduction

The endoplasmic reticulum (ER) is an organelle consisting of various structures in the form of interconnected channels and sacs in the cell [1]. The ER has various functions in the cell, such as being responsible for lipid synthesis, carbohydrate metabolism, calcium storage, and protein trafficking. Since it performs these

tasks, it is of great importance that the ER function is normal [2]. Excess nutrient intake or exceeding the working capacity of the ER for various reasons causes the accumulation of misfolded proteins in the ER, and thus the deterioration of ER homeostasis due to difficulties in meeting the demand [3]. As a result of this situation, a situation called ER stress occurs. Recently, the number of studies on this subject has been increasing due to the prevalence of ER stress. If ER stress is excessive, apoptosis occurs because the cell cannot adapt [4]. It has been determined that ER stress triggers many diseases in the organism. These diseases include obesity, diabetes, ischemia-reperfusion diseases, and neurodegenerative diseases [5]. Neurodegenerative diseases are very diverse and affect human health negatively [6]. In addition, the first is an attractive topic because the treatment of neurodegenerative diseases is limited [7]. Parkinson's, Alzheimer's, and Huntington's are among these harvests [8, 9]. In the diseases mentioned, some histopathological changes occur in various parts of the brain. Our aim in this study is to describe the definition of ER stress, the mechanisms of ER stress, the relationship of ER stress with neurodegenerative diseases, and the specific histopathological changes that occur in these diseases.

2. Endoplasmic reticulum stress

As we mentioned earlier, increased metabolic demand, infection, hypoxia, excessive lipid accumulation, genetic disorders, and various toxins can disrupt ER homeostasis and cause ER stress due to misfolded or unfolded protein accumulation [6]. To reduce ER stress, a signaling pathway called the unfolded protein response (UPR) is activated, which slows protein synthesis and increases protein degradation [7, 8]. Activated UPR creates a stress response via protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) [9, 10], inositol-requiring enzyme 1 (IRE-1) [10–12], and activating transcription factor 6 (ATF-6) [13, 14]. IRE1 acts by activating Jun N-terminal kinase (JNK) [15]. ATF-6 increases the expression of the X-box binding protein 1 (XBP-1s) factor in the nucleus [16]. XBP-1s binds to some genes containing DNA regions, and in ER expansion, folding capacity is increased. It stimulates the transcription of genes involved in the ER-related degradation pathway and the activation of the ER-related degradation pathway, and the demand load on the ER is alleviated. With this mechanism, unfolded proteins are degraded. When this function fails, the ER activates the nuclear factor kappa B (NF-kB) to produce a signal in the cell [15]. After this signal, some apoptotic genes are stimulated and apoptosis is triggered by the stimulated genes.

2.1 Activation of PERK (protein kinase R (PKR)-like endoplasmic reticulum kinase)

PERK activation plays an important role in ER stress [17]. PERK has a specific binding site for GRP78, a chaperone involved in protein folding known as 78-kDa glucose-regulated protein (GRP78/BIP) [18]. After unfolded or misfolded proteins accumulate in the lumen, GRP78 separates from PERK and causes PERK to oligomerize [19]. Then, PERK activates itself. Then, PERK phosphorylates eukaryotic initiation factor 2 (eIF2α) [20]. While eIF2α is phosphorylated, it remains bound to eIF2B, which acts as GEF, thus preventing the formation of the translation initiation complex eIF2α/GTP/Met-tRNAi [21]. Phosphorylation of eIF2α under ER stress stimulates the translation of the transcription factor ATF-4, which plays a role in the ER stress response [18].

2.2 Activation of ATF-6 (activating transcription factor-6)

ATF-6 is a trans-membrane protein involved in ER stress [22]. After protein folding in the ER is inhibited, ATF-6 migrates to the Golgi apparatus. GRP78 is involved in this event [23]. There are GLS1 and GLS2 structures on ATF-6, which are involved in adhesion to the Golgi [24]. When GRP78 is bound to GLS1, it retains ATF-6 in the ER membrane [25]. If there is unfolded protein in the lumen, GRP78 dissociates from GLS1, and thus GLS2 is activated and migrates to ATF-6 Golgi [13]. In the Golgi, the transmembrane region of ATF-6 is cut, and eventually, the systolic bZIP region of ATF-6 travels to the nucleus and stimulates the transcription of XBP-1 [14]. The XBP-1s form of XBP-1 stimulates the transcriptional responses of the UPR. Thus, it reduces long-term ER stress [25].

2.3 Activation of IRE-1 (inositol-requiring enzyme 1)

IRE-1 is an ER transmembrane protein. In the ER stress state, IRE-1 is activated due to the cleavage of GRP78 and stimulates XBP-1 activation [26]. This stimulates the activation of XBP-1 s. XBP-1 s play a role in the differentiation of cells by increasing the transcription of genes responsible for ER expansion so that cells can respond to the increased demands of protein synthesis and modification [15]. XBP-1s travels to the nucleus and upregulates the transcription of genes involved in phospholipid synthesis, which drives ER-related degradation and expansion [27]. It also plays a role in the activation of IRE-1 and the activation of the JNK signaling pathway [28]. IRE-1 interacts with TNF receptor-associated factor 2 (TRAF2), activating its downstream signaling. TRAF2 then binds to ASK1, and ASK1 phosphorylates and activates JNK [26]. This effect of IRE-1 provides a bridge between ER stress, growth factors, and mitogens [15] (**Figure 1**).

2.4 ER functions and relations with organelles

The endoplasmic reticulum (ER) is a cytoplasmic organelle responsible for cytoplasmic protein synthesis [30]. The ER has many vital cellular functions, such as lipid and steroid synthesis, Ca2+ homeostasis and storage, carbohydrate metabolism, and protein synthesis [31]. With these features, the ER provides internal connection and coordination with other organelles and many proteins and physical structures in the cell. Therefore, they are in multiple contacts with all membrane-bound organelles, including the ER, plasma membrane (PM), mitochondria, Golgi, endosomes, and peroxisomes [30].

2.5 ER and plasma membrane (PM)

The ER acts as a Ca2+ store in the cell and has dynamic communication with the PM. Contact sites between ER and PM play a role in Ca2+ exchange. At ER-PM junctions, stromal interacting molecule (STIM) proteins sense a decrease in ER Ca2+ levels, undergo a conformational change along the ER that repositions tubular structures to ER-PM, and directly activate Orai, the pore-forming component of Ca2 + −. The release-activated Ca2 + (CRAC) channel triggers channel opening and Ca2+ influx [32]. In addition, ER-PM contact sites are important for phosphatidylinositol metabolism, particularly for the regulation of the lipid signaling molecule phosphatidylinositol 4-phosphate (PI4P) [30].

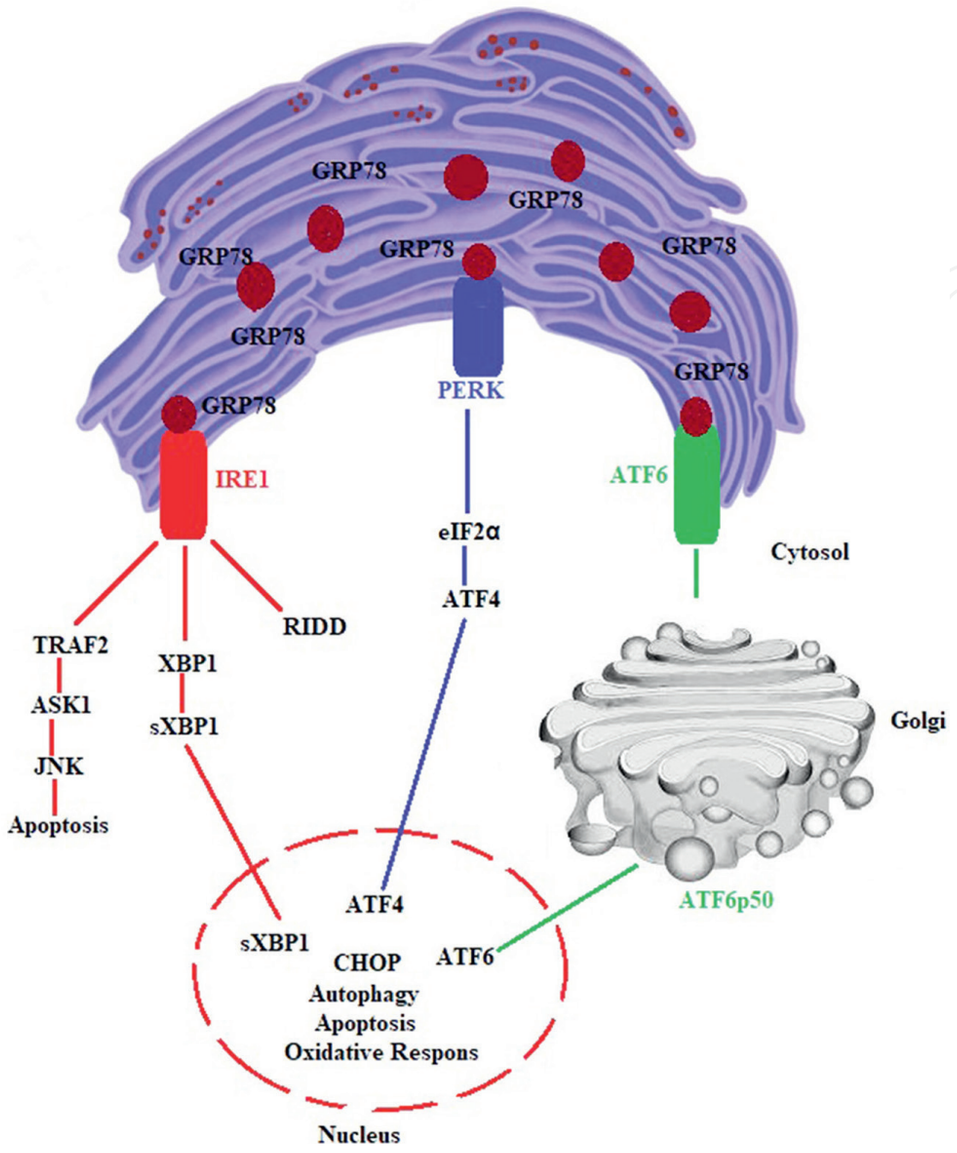

Figure 1.
Effective pathways in the ER stress response [29].

2.6 ER and mitochondria

Considering the relationship between the endoplasmic reticulum and mitochondria, there is a membrane that provides the connection between the ER and the mitochondria [30]. This membrane has been named the mitochondria-associated ER membrane (MAM). Communication between the ER and the mitochondria is provided by this membrane. This communication is very important for the survival of the cell. Many functions such as lipid transfer, autophagosome formation, mitochondrial fission, Ca2+ homeostasis, and apoptosis are regulated by this communication [33]. In this contact zone, calcium influx occurs into the intermembrane space and the mitochondrial matrix. It has been stated that changes in Ca2+ levels occur in case of disturbance in the regulation of this flow, thus affecting apoptosis, mitochondrial division, and motility, and altering the activity of mitochondrial Ca2+ binding proteins [34]. As a result, ER and mitochondrial communication disorders lead to a number of problems such as mitochondrial damage, Ca2+ dyshomeostasis, ER stress,

defects in lipid metabolism, autophagy, decreased respiratory chain activity, and oxidative phosphorylation [35]. It has been determined that the communication disorder between these two organelles plays an important role in the regulation of neurological activity. It has been determined that the relationship between these organs is impaired in Alzheimer's, Parkinson's, and Huntington's disease [36].

3. ER stress and the unfolded protein response (UPR)

The ER is the main region in the cell where protein synthesis and post-synthesis changes take place, where newly synthesized proteins are folded and combined. The ER is extremely sensitive to many factors that will affect this function [37]. In case of any problem, misfolded or unfolded proteins begin to accumulate in the cytoplasm. When the protein concentration accumulated in the cytoplasm increases, the ER cannot cope with this load, and this causes the functioning to be worse [38]. Eukaryotic cells can adapt by reducing the rate of protein synthesis, upregulating the expression of genes encoding chaperones and other proteins that prevent polypeptide aggregation, and disrupting accumulated misfolded proteins. This set of cellular responses is obtained after activation of an integrated intracellular signaling cascade: the "Unfolded Protein Response" (UPR) [39]. The UPR is regulated by three sensor proteins known as PERK (PKR-like ER kinase), IRE1_ (inositol-requiring transmembrane kinase/endoribonuclease 1), and ATF6 (activating transcription factor 6). These proteins are associated with BiP or GRP78 (78 KDa glucose-regulated protein) and therefore remain inactive [29]. BiP is released under ER stress, and the response is shaped by further dimerization and autophosphorylation of PERK and IRE1 [40, 41]. The UPR cascade is activated after regulated intramembrane proteolysis of another regulatory sensor protein, ATF6, against the UPR [42] (**Figure 2**).

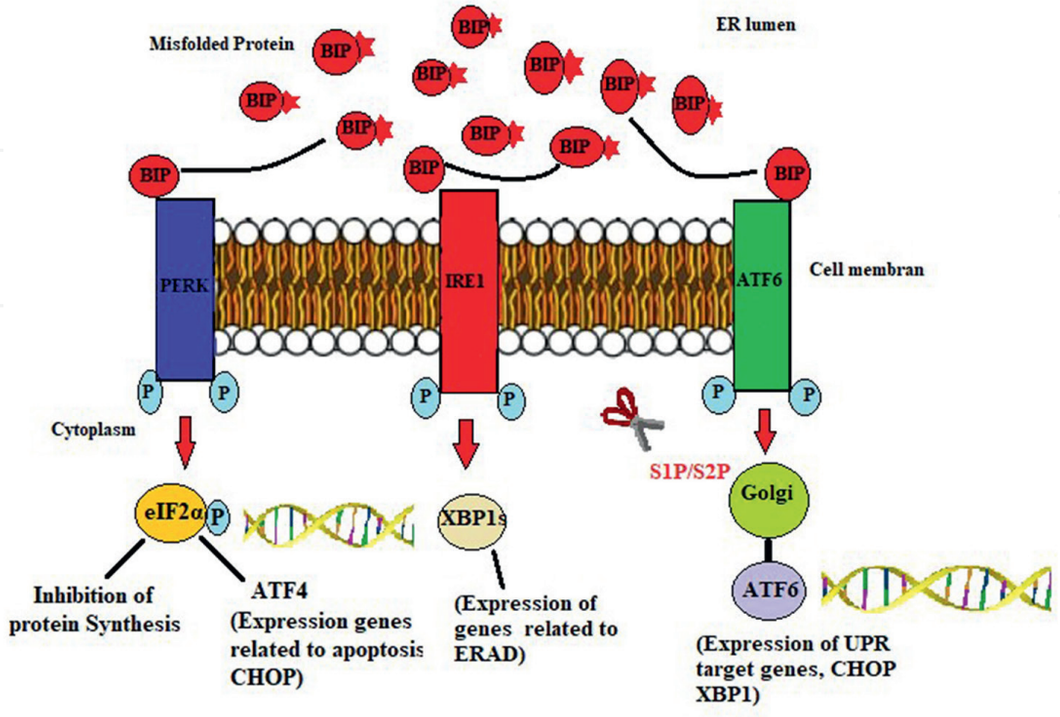

Figure 2.
The UPR. UPR is controlled by three sensor proteins [43].

4. Endoplasmic reticulum (ER) stress response and histopathological changes in Parkinson's disease

Parkinson's disease is a neuropathological disease involving the degeneration of dopaminergic neurons in the substantia nigra followed by loss of their terminals in the striatum [44]. The main clinical manifestations are resting tremor, bradykinesia, rigidity, and postural reflex dysfunction [44]. Currently, the cause of nigral degeneration, which is responsible for the development of the symptoms of this disease, is unknown. However, considering the studies, it is thought that hereditary predisposition, environmental toxins, and aging play an important role in this process and multifactorial causes come to the fore in etiopathogenesis. Various studies have shown that ER stress plays an essential role in the pathophysiology of Parkinson's [45]. ER stress occurs when protein aggregates and fibril accumulation in the Parkin cell with increased ROS in Parkinson's disease. In a study, it was reported that ER stress occurred in the cell culture medium. In another study, UPR components such as transcriptional factors and CHOP and ER chaperones in neurons cause damage to cells [45, 46]. It has also been stated that IRE, PERK, and ER stress kinase phosphorylation, which are involved in ER stress, play a role in Parkinson's and cause the degeneration of dopaminergic neurons [47]. Again, as a result of some studies, it has been reported that 6-OHDA and MPP+ applied to create experimental Parkinson's show their effects by triggering the UPR increase in neurons.

Characteristic features of Parkinson's disease include loss of neurons in certain areas of the brain region called the substantia nigra and extensive accumulation of intracellular protein (alpha-synuclein) [48]. While the loss of pigmented dopaminergic neurons in the substantia nigra and accumulation of α-synuclein in neurons are not specific for Parkinson's disease, these two major neuropathologies, when observed together, are specific for definitive diagnosis of idiopathic Parkinson's disease [49, 50].

5. Endoplasmic reticulum (ER) stress response and histopathological changes in Alzheimer's disease

Alzheimer's disease is the most common type of dementia. It is a progressive disease that begins with mild memory loss, possibly leading to loss of the ability to maintain speech and react to the environment [51]. Alzheimer's disease involves parts of the brain that control thought, memory, and language. As a result of studies on Alzheimer's, he stated that ER stress plays a vital role in the pathogenesis of Alzheimer's [52, 53]. Some studies determined that Ca homeostasis and accumulation of phosphorylated tau protein and intracellular amyloid-β play an important role in this disease. Again, some studies have shown that pPERK, pIRE1, and elF2α, which are the kinases of the UPR, are increased in the hippocampus and brain tissue neurons of Alzheimer's patients [54]. Again, PERK, eIF2α, and p38 MAPK activation associated with the presence of tau protein were observed in Alzheimer's patients. These findings clearly demonstrated the relationship between tau proteins in neurons and ER stress. In some studies, it has been stated that Alzheimer's disease increases as a result of cerebral ischemia or stroke. This is a clear indication that aging impairs the folded protein response by disrupting ER homeostasis due to oxidative stress and plays a role in the pathogenesis of the disease. Some studies on the UPR have reported increased levels of BIP/GRP78, protein kinase, and PERK in the brain of Alzheimer's patients [55].

The ER stress-mediated inflammatory response has an important role in Alzheimer's disease pathogenesis. The inflammatory response is normally triggered by the activation of inflammatory receptors, including TLRs (toll-like receptors) and NLRs (NOD-like receptors). These pattern recognition receptors transduce the signaling mostly via the NF-κB pathway and trigger the inflammatory response [56]. Additionally, the ER stress-mediated inflammatory response has a role in the pathogenesis of some diseases [57]. In obesity, ER stress can induce an inflammatory response and cause peripheral insulin resistance [58], and in the liver, ER stress can trigger the systemic inflammatory response and cause damage [59]. In neurodegenerative diseases, inflammatory processes are initiated by the maturation of the IL-1 cytokines called as inflammasomes [60].

Histopathologically senile amyloid in Alzheimer's disease plaques (SAP), neurofibrillary flock (NF) formation, loss of synapsneurons, and marked atrophy in the brain are detected [51]. The formation of senile plaques is the most important histopathological finding of the disease. It is a symptom of the disease and is seen especially in the amygdala, hippocampus, and neocortex. On the other hand, NF is required for the definitive diagnosis of AD [52]. And the detection of SPs is necessary but not sufficient. Both lesions occur both in normal aging and in some and can be seen in other neurodegenerative diseases. AD for the definitive diagnosis of NFY and SAP is a certain neuroanatomical. They must be shown to be in the distribution and in certain quantities [53].

6. Endoplasmic reticulum (ER) stress response and histopathological changes in Huntington's disease

Huntington's disease is a progressive and fatal neurodegenerative disease, and the mechanism that causes neuronal apoptosis has not been fully elucidated [61]. Studies have shown that ER stress, which occurs as a result of misfolded protein accumulation, which may contribute to neuronal loss, may play a role [62]. Although different studies have shown a role for the UPR in HD, the evidence is inconclusive [63]. In a study, RAB5A, HMGB1, CTNNB1, DNM1, TUBB, TSG101, EEF2, DYNC1H1, SLC12A5, ATG5, AKT1, CASP7, and SYVN1 genes were identified, which would suggest a potential link between UPR and Huntington's disease [64, 65]. A significant association was found in the length of the polyglutamine pathway of Huntington, which is a critical determinant of disease onset in human HD patients and points to the UPR as a promising target for therapeutic intervention [66].

The most affected region in terms of histopathological changes in HD is the striatal region. However, it was determined that gray and white matter were affected in cortical and noncortical areas. In addition, aggregates/inclusions are characteristic histopathological markers of HD.

7. Conclusion

As a result, the accumulation of unfolded or misfolded proteins in the cytosol under ER stress is an important mechanism in the occurrence of cell damage. PERK IRE1, and ATF6, which sense this protein folding response, play an important role in shaping the cellular pathway. In addition, the relationship between ER stress and mitochondria is important in the maintenance of cellular response. ER stress plays

an important role in the pathogenesis of many neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's. Knowing the histopathological changes seen in these diseases is very important in the diagnosis of the disease. The role of misfolded or unfolded protein response in ER stress in neurodegenerative diseases, and the histopathological changes in these diseases will help to develop therapeutics for neurodegenerative diseases.

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References

[1] Wu J, Kaufman RJ. From acute ER stress to physiological roles of the unfolded protein response. Cell Death and Differentiation. 2006;**13**:374-384

[2] Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. Nature Reviews. Molecular Cell Biology. 2007;**8**:519-529

[3] Lee AS. The glucose-regulated proteins: Stress induction and clinical applications. Trends in Biochemical Sciences. 2001;**26**:504-510

[4] Ledoux S, Yang R, Friedlander G, et al. Glucose depletion enhances P-glycoprotein expression in hepatoma cells: Role of endoplasmic reticulum stress response. Cancer Research. 2003;**63**:7284-7290

[5] Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: Cell life and death decisions. The Journal of Clinical Investigation. 2005;**115**:2656-2664

[6] Caughey B, Lansbury PT. Protofibrils, pores, fibrils, and neurodegeneration: Separating the responsible protein aggregates from the innocent bystanders. Annual Review of Neuroscience. 2003;**26**:267-298

[7] Cavedo E, Lista S, Khachaturian Z, et al. The road ahead to cure Alzheimer's disease: Development of biological markers and neuroimaging methods for prevention trials across all stages and target populations. The Journal of Prevention of Alzheimer's Disease. 2014;**1**(3):181-202

[8] Cho KJ, Lee BI, Cheon SY, et al. Inhibition of apoptosis signal-regulating kinase 1 reduces endoplasmic reticulum stress and nuclear huntingtin fragments in a mouse model of Huntington disease. Neuroscience. 2009;**163**(4):1128-1134

[9] Chung CY, Khurana V, Auluck PK, et al. Identification and rescue of α-synuclein toxicity in Parkinson patient–derived neurons. Science. 2013;**342**(6161):983-987

[10] Urano F, Bertolotti A, Ron D. Ire1 and efferent signaling from the endoplasmic reticulum. Journal of Cell Science. 2000;**113**:3697-3702

[11] Boot-Handford R, Briggs MD. The unfolded protein response and its relevance to connective tissue diseases. Cell and Tissue Research. 2010;**339**:197-211

[12] Acosta-Alvear D, Zhou Y, Blais A, et al. Xbp1 controls diverse cell type- and condition-specific transcriptional regulatory networks. Molecular Cell. 2007;**27**:53-66

[13] Haze K, Yoshida H, Yanagi H, et al. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. Molecular Biology of the Cell. 1999;**10**:3787-3799

[14] Haze K, Okada T, Yoshida H, 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. The Biochemical Journal. 2001;**355**:19-28

[15] Gardner BM, Walter P. Unfolded proteins are Ire1- activating ligands that

directly induce the unfolded protein response. Science. 2011;**333**:1891-1894

[16] Yoshida H, Matsui T, Yamamoto A, et al. 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

[17] Shin BS, Maag D, Roll-Mecak A, et al. Uncoupling of initiation factor eIF5B/IF2 GTPase and translational activities by mutations that lower ribosome affinity. Cell. 2002;**111**:1015-1025

[18] Lu PD, Harding HP, Ron D. Translation reinitiation at alternative open reading frames regulates gene expression in an integrated stress response. The Journal of Cell Biology. 2004;**167**:27-33

[19] Halperin L, Jung J, Michalak M. The many functions of the endoplasmic reticulum chaperones and folding enzymes. IUBMB Life. 2014;**66**:318-326

[20] Novoa I, Zeng H, Harding HP, et al. Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2alpha. The Journal of Cell Biology. 2001;**153**:1011-1102

[21] Wang XZ, Ron D. Stress-induced phosphorylation and activation of the transcription factor CHOP (GADD153) by p38 MAP kinase. Science. 1996;**272**:1347-1349

[22] Haas IG, Wabl M. Immunoglobulin heavy chain binding protein. Nature. 1983;**306**:387-389

[23] Munro S, Pelham HR. An Hsp70-like protein in the ER: Identity with the 78 kd glucose-regulated protein and immunoglobulin heavy chain binding protein. Cell. 1986;**46**:291-300

[24] Normington K, Kohno K, Kozutsumi Y, et al. S. cerevisiae encodes an essential protein homologous in sequence and function to mammalian BiP. Cell. 1989;**57**:1223-1236

[25] Pouyssegur J, Shiu RP, Pastan I. Induction of two transformation- sensitive membrane polypeptides in normal fibroblasts by a block in glycoprotein synthesis or glucose deprivation. Cell. 1977;**11**:941-947

[26] Nishitoh H, Matsuzawa A, Tobiume K, et al. HAsk1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. Genes & Development. 2002;**16**:1345-1355

[27] Hetz C, Glimcher LH. Fine-tuning of the unfolded protein response: Assembling the IRE1 alpha interactome. Molecular Cell. 2009;**35**:551-561

[28] Upton JP, Wang L, Han D, et al. Ire1alpha cleaves select microRNAs during ER stress to derepress translation of proapoptotic caspase-2. Science. 2012;**338**:818-822

[29] Xiang C, Wang Y, Zhang H, Han F. The role of endoplasmic reticulum stress in neurodegenerative disease. Apoptosis. 2017;**22**(1):1-26

[30] English AR, Voeltz GK. Endoplasmic reticulum structure and interconnections with other organelles. Cold Spring Harbor Perspectives in Biology. 2013;**5**:a013227

[31] Schwarz DS, Blower MD. The endoplasmic reticulum: Structure, function and response to cellular signaling. Cellular and Molecular Life Sciences. 2016;**73**:79-94

[32] Burgoyne T, Patel S, Eden ER. Calcium signaling at ER membrane contact sites. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2014;**1853**:2012-2017

[33] Xia MF, Zhang YZ, Jin K, Lu ZT, Zeng Z, Xiong W. Communication between mitochondria and other organelles: A brand-new perspective on mitochondria in cancer. Cell & Bioscience. 2019;**9**:1-19

[34] Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J, Voeltz GK. ER tubules mark sites of mitochondrial division. Science. 2011;**334**:358-362

[35] Area-Gomez E, De Groof A, Bonilla E, Montesinos J, Tanji K, Boldogh I, et al. A key role for MAM in mediating mitochondrial dysfunction in Alzheimer disease. Cell Death & Disease. 2018;**9**:1-10

[36] Gómez-Suaga P, Bravo-San Pedro JM, González-Polo RA, Fuentes JM, Niso-Santano M. ER-mitochondria signaling in Parkinson's disease review-article. Cell Death & Disease. 2018;**9**:1-12

[37] Uddin MS, Tewari D, Sharma G, Kabir MT, Barreto GE, Bin-Jumah MN, et al. Molecular mechanisms of ER stress and UPR in the pathogenesis of Alzheimer's disease. Molecular Neurobiology. 2020;**57**:1-18

[38] Carrara M, Prischi F, Nowak PR, Kopp MC, Ali MMU. Noncanonical binding of BiP ATPase domain to Ire1 and Perk is dissociated by unfolded protein CH1 to initiate ER stress signaling. eLife. 2015;**4**:e03522

[39] Hu H, Tian M, Ding C, Yu S. The C/EBP homologous protein (CHOP) transcription factor functions in endoplasmic reticulum stress-induced apoptosis and microbial infection. Frontiers in Immunology. 2019;**10**:1-13

[40] Ron D, Hubbard SR. How IRE1 reacts to ER stress. Cell. 2008;**132**:24-26

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

[42] Hollien J, Lin JH, Li H, Stevens N, Walter P, Weissman JS. Regulated Ire1-dependent decay of messenger RNAs in mammalian cells. The Journal of Cell Biology. 2009;**186**:323-331

[43] Ghemrawi R, Khair M. Endoplasmic reticulum stress and unfolded protein response in neurodegenerative diseases. International Journal of Molecular Sciences. 2020;**21**(17):6127

[44] Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology. 2007;**68**:326-337

[45] Bellucci A, Navarria L, Zaltieri M, Falarti E, Bodei S, Sigala S, et al. Induction of the unfolded protein response by α-synuclein in experimental models of Parkinson's disease. Journal of Neurochemistry. 2011;**116**:588-605

[46] Bellani S, Mescola A, Ronzitti G, Tsushima H, Tilve S, Canale C, et al. GRP78 clustering at the cell surface of neurons transduces the action of exogenous alpha-synuclein. Cell Death and Differentiation. 2014;**21**:1971-1983

[47] Valdés P, Mercado G, Vidal RL, Molina C, Parsons G, Court FA, et al. Control of dopaminergic neuron survival by the unfolded protein response transcription factor XBP1. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**:6804-6809

[48] Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy pathology. Nature Reviews. Neurology. 2013;**9**:13-24

[49] Witt SN. Molecular chaperones, α-synuclein, and neurodegeneration. Molecular Neurobiology. 2013;**47**:552-560

[50] Malek N, Swallow D, Grosset KA, Anichtchik O, Spillantini M, Grosset DG. Alpha-synuclein in peripheral tissues and body fluids as a biomarker for Parkinson's disease—A systematic review. Acta Neurologica Scandinavica. 2014;**130**:59-72

[51] Santos LE, Ferreira ST. Crosstalk between endoplasmic reticulum stress and brain inflammation in Alzheimer's disease. Neuropharmacology. 2018;**136**:350-360

[52] Lindholm D, Wootz H, Korhonen L. ER stress and neurodegenerative diseases. Cell Death and Differentiation. 2006;**13**:385-392

[53] Mattsson N, Zetterberg H, Janelidze S, Insel PS, Andreasson U, Stomrud E, et al. Plasma tau in Alzheimer disease. Neurology. 2016;**87**:1827-1835

[54] Devi L, Ohno M. PERK mediates eIF2αphosphorylation responsible for BACE1 elevation, CREB dysfunction and neurodegeneration in a mouse model of Alzheimer's disease. Neurobiology of Aging. 2014;**35**:2272-2281

[55] O'Connor T, Sadleir KR, Maus E, Velliquette RA, Zhao J, Cole SL, et al. Phosphorylation of the translation initiation factor eIF2α increases BACE1 levels and promotes Amyloidogenesis. Neuron. 2008;**60**:988-1009

[56] Lee MS, Kim YJ. Signaling pathways downstream of pattern recognition receptors and their cross talk. Annual Review of Biochemistry. 2007;**76**:447-480

[57] Lin JH, Walter P, Yen TSB. Endoplasmic reticulum stress in disease pathogenesis. Annual Review of Pathology. 2008;**3**:399-425

[58] Hotamisligil GS. Role of endoplasmic reticulum stress and c-Jun NH2-terminal kinase pathways in inflammation and origin of obesity and diabetes. Diabetes. 2005;**54**(Suppl. 2):S73-S78

[59] Bailey D, O'Hare P. Transmembrane bZIP transcription factors in ER stress signaling and the unfolded protein response. Antioxidants & Redox Signaling. 2007;**9**:2305-2321

[60] Todd DJ, Lee AH, Glimcher LH. The endoplasmic reticulum stress response in immunity and autoimmunity. Nature Reviews. Immunology. 2008;**8**:663-674

[61] Leitman J, Ulrich Hartl F, Lederkremer GZ. Soluble forms of polyQ-expanded huntingtin rather than large aggregates cause endoplasmic reticulum stress. Nature Communications. 2013;**4**:2753

[62] Duennwald ML, Lindquist S. Impaired ERAD and ER stress are early and specific events in polyglutamine toxicity. Genes & Development. 2008;**22**(23):3308-3319

[63] Yang H, Liu C, Zhong Y, 6Luo S, Monteiro MJ, Fang S. Huntingtin interacts with the cue domain of gp78 and inhibits gp78 binding to ubiquitin and p97/VCP. PLoS One. 2010;**5**(1):e8905

[64] Carnemolla A, Fossale E, Agostoni E, Michelazzi S, Calligaris R, De Maso L, et al. Rrs1 is involved in endoplasmic reticulum stress response in Huntington

disease. The Journal of Biological Chemistry. 2009;**284**(27):18167-18173

[65] Reijonen S, Putkonen N, Norremolle A, Lindholm D, Korhonen L. Inhibition of endoplasmic reticulum stress counteracts neuronal cell death and protein aggregation

[66] Leitman J, Barak B, Benyair R, Shenkman M, Ashery U, Hartl FU, et al. ER stress-induced eIF2-alpha phosphorylation underlies sensitivity of striatal neurons to pathogenic huntingtin. PLoS One. 2014;**9**(3):e90803