Chapter

Endoplasmic Reticulum Stress-Mediated Cell Death

Mehtap Kara and Ezgi Oztas

Abstract

In normal functioning cells, endoplasmic reticulum (ER) is the major control site for folding, modification, and trafficking of secretory and cell-surface proteins. ER also plays a crucial role in the maintenance of cellular calcium homeostasis. Since ER is a key organelle in the cell; ER stress-mediated cell death can be associated with numerous diseases including Alzheimer disease, Parkinson disease, neuronal damage-induced ischemia, prion disease, cystic fibrosis, and diabetes mellitus. ER stress is a consequence of complex mechanisms which several cellular pathways interact with each other simultaneously. The two most important initiating points for ER stress-mediated cell death are; transcription factor CHOP/GADD153 and ER membrane protein kinase (IRE1). ER stress triggers proteolytic cleavage of caspase-12 and caspase-4, both of which are localized at the cytoplasmic side of the ER membrane to initiate the mechanism of cell death. Thus, ER stress and mitochondrial apoptosis are linked via caspase-12, which is seen in several degenerative diseases.

Keywords: endoplasmic reticulum stress, unfolded protein response signaling, autophagy, endoplasmic reticulum stress mediator proteins, endoplasmic reticulum stress-mediated diseases

1. Introduction

The endoplasmic reticulum (ER) is an intracellular organelle which has many roles in calcium storage, protein synthesis, degradation and transport, and carbohydrate and lipid metabolism. The ER has different types of domains in its specialized units to ensure its multifunction. The main function of the ER is the synthesis of secreted, cytosolic and membrane proteins. These processes are controlled by ribosomes that are localized in the cytosolic site of the ER. Initially, ribosomes and mRNA are united to form a translational complex on the inner surface of the cytosolic site of the ER. The protein synthesis starts in the cytosol and continues in mRNA-ribosome-signal recognition particle (SRP) complexes that are located on the ER membrane. Proteins classified simultaneously with protein synthesis are guided to the membrane or Golgi apparatus for secretion. The terminal step of the protein synthesis is the cleavage of the signal peptide; after this phase, proteins are secreted from the ER membrane to the cytosol via ribosomes [1, 2]. Between synthesis and secretion, exocrine proteins require folding and modifications through folding enzymes and chaperons. N-linked glycosylation, disulfide bond formation and oligomerization of proteins are determinants of the secretory proteins which indicates if they are or not [3, 4]. Hereby, the ER is one of the most crucial and multifunctional organelles for cell survival.

Since alterations of the ER's functions leads to unfolded and/or misfolded proteins in the cell, ER stress-mediated cell death underlie several serious diseases such as cardiovascular disease, neurodegeneration, ischemia and diabetes. Stress conditions are captured by transmembrane receptors which are localized on the ER and unfolded protein response (UPR) initiated by these receptors. Under chronic stress conditions, the adaptive response of the ER fails and the cells undergo mechanisms of cell death. In the ER stress conditions ATP, calcium and oxidizing environment are important factors for protein folding and disulfide bond formation. UPR is the major protective mechanism against deleterious and toxic effects of ER stress. Protein RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1 (IRE1α) are the tree main modulators of the ER stress response pathway [5, 6].

In a normal functioning cell PERK, ATF6 and IRE1 are in an inactive phase that is maintained by a specific ER chaperone, GRP78. When the ER stress is triggered, GRP78 is released to activate these three receptors as UPR. Unfolded protein stress has a crucial role in cell survival. However, the internal ribosomal entry site (IREs) bypasses the eukaryotic translation initiation factor 2α (eIF2α) controlling pathway. In the PERK-eIF2 pathway, activating transcription factor 4 (ATF4) is the key element which encodes cAMP response element-binding transcription factor (C/EBP) and promotes cell survival via modulation of redox reactions, stress response, protein synthesis and secretion. On the other hand ATF4 promotes C/EBP homologous protein (CHOP) which triggers apoptotic cell death. In the ER stress-mediated cell death, mitochondrial apoptotic pathway initiates the autophagy while other cell death mechanisms play a smaller role (**Figure 1**). It has been concluded that the ER stress-mediated cell death is associated with severe diseases including nervous system disorders, diabetes and cancer [7–10].

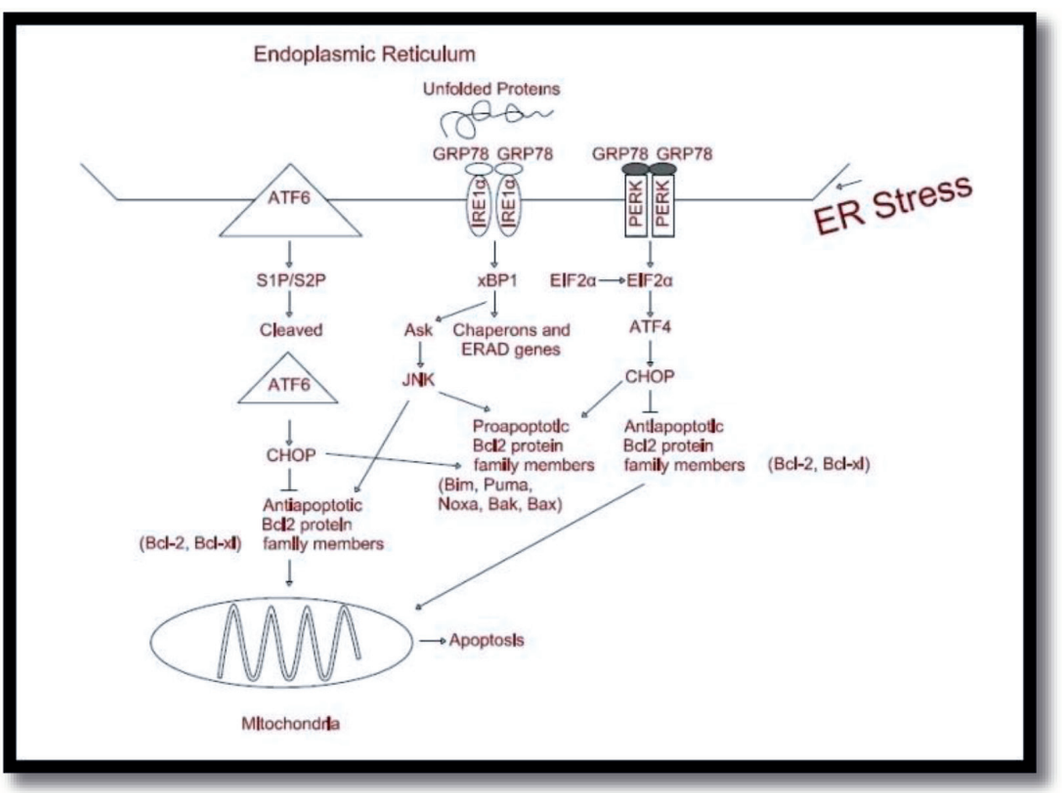

Figure 1.
ER stress-mediated pathways via PERK, IRE1α and ATF6 which stimulates apoptosis and suppress anti-apoptotic proteins.

2. Unfolded protein response (UPR) signaling

Several endogenous and exogenous factors may interfere with the ER protein folding mechanism and generate stress conditions which have been an issue of importance, strongly focused on in recent years. Chronic stress conditions may result with pathological perturbations in different systems in the organisms. Once the ER stress is triggered, UPR mechanisms strive to restore the ER homeostasis. If the UPR system does not be sufficient, apoptosis inducing signals are increased in the cell; and ultimately, cell death signaling pathways are activated [9, 10]. Enduring unfolded protein response (UPR) and ER stress in the cell cause dysfunctions of some mechanistic pathways which may in turn stimulate cell death. In the center of the UPR and ER stress response mechanism, IRE1α is placed as a key regulatory molecule. It has been demonstrated that IRE1α can directly bind to unfolded proteins and start signaling. IRE1α and its signaling pathway determine the fate of the cell between survival and death based on the longevity of ER stress [12].

PERK, ATF6 and IRE1 are the three main initiating proteins of UPR signaling due to ER stress. ATF6 is synthetized as an inactive precursor, and it contains bZIP transcription factor in its cytoplasmic domain. Under stress conditions, ATF6f, which is the active component of ATF6s, is released in the Golgi apparatus after cleavage by S1P and S2P proteases. ATF6f plays an important role as a transcription factor on ER homeostasis genes which include ER chaperons and ER-associated protein degradation (ERAD) [12–14]. PERK which is a transmembrane protein kinase gets in dimerization and auto-phosphorylation under ER stress conditions and phosphorylates eIF2α. Phosphorylated eIF2α have effects on initiating the selective translation of ATF4, protein folding factors genes expression regulation and plays a role in oxidative stress and amino acid metabolisms [14–16].

IRE1 is the most conserved signaling pathway in the ER stress mechanism. IRE1α and IRE1β are the main two isoforms of the IRE1. These isoforms have kinase and endoribonuclease activities at their cytoplasmic domain. Under stress conditions IRE1α goes into dimerization and auto-phosphorylation with a conformational change in its cytoplasmic part and activates the endoribonuclease domain. Active IRE1α catalyzes the splicing of X box-binding protein 1 (XBP-1) in its 26-nucleotide intron that result with active transcription factor XBP-1s which regulates protein folding, targeting to ER, ERAD and biogenesis of Golgi etc. [9, 16, 17]. IRE1α is a transmembrane protein that includes an N-terminal sensor domain, single transmembrane domain and C-terminal cytosolic effector domain. The C-terminal domain of IRE1α has both protein kinase and endoribonuclease activities. IRE1α oligomerization is induced by unfolded protein stress in the cell and following this cytosolic domain auto-phosphorylation occurs. With UPR control, IRE1α has an important cytoprotective effect [18, 19].

UPR signaling in the cell play an important role for restoring cellular homeostasis; however, chronic ER stress may result with cell death [11]. Apoptosis is the main cell death mechanism in ER stress; however, other types of cell death, such as necrosis, necroptosis or deregulated autophagy may contribute to ER stress too. Also autophagy that is a mechanism which enables the elimination of unfolded or misfolded proteins under ER stress conditions is one of the most studied issues in recent studies [20]. mRNA of IRE1α is regulated through X-box binding protein as well IRE1α controls its own mRNA expression by self-cleavage [21].

3. Cell death under endoplasmic reticulum stress conditions

3.1 PERK Signaling pathway

Under ER stress conditions, after activation of PERK, eIF2α phosphorilated by PERK and this phosphorylated eIF2α trigger translational arrest as a pro-survival response. This prosurvival response is important checkpoint step before cell death. Deficiencies of PERK expression or phosphorylation problems of eIF2α make cells more sensitive to ER stress conditions. PERK associated signaling pathway regulates important mechanisms such as autophagy, ATF4-mediated transcription pathway, and protein folding and redox metabolism [22, 23].

In different cell types it has been demonstrated that cell death is induced via the PERK signaling pathway under chronic stress conditions. The key molecule for initiating cell death is C/EBP homologous protein (CHOP), also named as growth arrest and DNA-damage-inducible 153 (GADD153). The expression of CHOPs is increased by ATF4. PERK activation induces eIF2α phosphorylation which in turn increases the selective transcription of ATF4 that increases CHOP level. Pro-apoptotic proteins such as GADD34, ERO1α (ER oxidase 1 alpha) and BH3-only proteins (BIM, PUMA and NOXA) expressions is increased by CHOP. PERK signaling pathway initiates mitochondrial apoptotic pathway. GADD34 and Ero1α increase cellular ROS production and calcium. Calcium release is regulated by IPR3 and the increase of cytosolic calcium triggers PTP related apoptosis in the cell. On the other hand, BIM, PUMA and NOXA induction cause cytochrome-c release from mitochondria via BAX and BAK activation [23–26].

CHOP, main member of Bcl-2 family, is one of the ER stress associated regulator molecule which downregulates Bcl-2. Another member of Bcl-2 family is BH3-only proteins which are pro-apoptotic proteins and upregulated by CHOP. Moreover, CHOP induces BIM, PUMA and NOXA expression levels [27–29]. CHOP has another important role in the ER as a modulator of oxidative status in the organelle. Increase in the level of CHOP and ERO1α in the cell causes a decrease of the glutathione (GSH) level which leads to ROS formation. ERO1α induces reduction of hydrogen peroxide (H_2O_2) in the ER lumen via reconstitution of the active state of proteins through re-oxidation of protein disulfide isomerases (PDIs). Increased ROS conditions in the cell via ER stress make cells sensitive to cell death. Moreover, CHOP increase in the cell triggers the activation of inositol- 1,4,5-trisphosphate receptor (IP3R) through ERO1α and calcium release from ER to cytosol which contribute to apoptosis. Thus, PERK plays a key role in inducing cell death via ROS production and calcium release. It has been demonstrated that, apoptosis can be induced without activation of the PERK signaling pathway; because, there are several triggers of apoptosis in different conditions. It has been reported in different studies that, PERK signaling deficiencies may play a role in different types of diseases such as Parkinson disease, diabetes, atherosclerosis, ALS, cardiac dysfunction and liver damage induced by alcohol. Further and detailed studies are needed to clarify the full mechanism of the ER stress dependent disease occurrence [24, 26, 30–35].

3.2 IRE1 signaling pathway

IRE1α/XBP-1 pathway plays a balancing role in survival-cell death homeostasis and also takes part in the gene regulation of the protein folding elements. With ER stress ASK1/JNK or NF-κB signaling pathways get activated by IRE1α-TRAF2 complex and afterwards cell death processes as apoptosis or autophagy starts in the cell [36–39]. IRE1α-dependent decay (RIDD) is IRE1α's endoribonuclease activity on several mRNAs. RIDD mechanism has a defensive role for degradation of proteins

which have a misfolding potential and also RIDD takes part in pro-apoptotic mechanisms too. RIDD mechanism shows its pro-apoptotic effects through ER chaperons BiP/Grp78 mRNA degradation, effecting JNK signaling pathway or XBP-1 mRNA splicing. Thus, RIDD is placed in the center of the ER stress-mediated cell death and cell survival. It has been recently demonstrated that IRE1α show its endoribonuclease activity on different microRNAs (miRNA), caspase-2 and TXNIP which have role in cell death processes [40–42].

Dimerization, auto-phosphorylation and endoribonuclease domain engaging of IRE1α occurs under stress conditions. Active IRE1α activates transcription factor XBP1 which is named as XBP1s. XBP1 has a regulative role in protein folding [11, 12].

IRE1 contains a serine-threonine kinase and an endoribonuclease domain. With its endonuclease activity, IRE1 splices the 26-nucleotide intron from ATF6-induced XBP1 mRNA which generates the frameshift splice variant as sXBP1 and this variant encodes stable and active transcription factor. zXBP1 targets are ER chaperons and P58IPK which belongs to the HSP40 family. P58IPK plays a role in the negative feedback mechanism of PERK through binding and inhibiting PERK. P58IPK activity has the power to finish the UPR if the UPR could evade the ER stress, if not, the P58IPK activity gets suppressed and the apoptotic mechanism starts in the cell. Generally, IRE1 release has a strong pro-survival effect during stress conditions via UPR; however, long term active IRE induces kinase activities through the c-Jun N-terminal kinase (JNK) pathway and recruitment of TNF-receptor-associated factor 2 molecule (TRAF2). The IRE1-TRAF2 complex causes recruitment of apoptosis-signal-regulating kinase (ASK1) which in turn activates MAPKs JNK and p38. JNK activation associated with Bcl2 family members' regulation in different stress conditions. During ER stress JNK phosphorylates the Bcl2 and inhibits its anti-apoptotic function, however while JNK phosphorylates Bcl-2 homology domain 3 (BH3) and Bim, their pro-apoptotic features gets activated. As an important initiator of apoptosis, IRE1 is the last resorts for the ER stress regulated UPR after PERK and ATF6. IRE1 is the top step for modulation of pro-surviving or cell-death in the cell via ASK1 and JNK [5, 43].

3.3 ATF6 signaling pathway

GRP78 is one of the main regulatory proteins for the ER stress pathways, while ATF6 is separated from GRP78, ATF6 translocate to Golgi apparatus to get spliced from its active sites. Active ATF6 in turn enhance the gene expressions of stress response elements in the nucleus. GRP78, GRP94, protein disulfide isomerase, CHOP and XBP1 are some of the targets of ATF6. However, ATF6-mediated cell death mechanism has not been clarified yet and further studies are needed to explain detailed intracellular protein interactions [5].

ATF6 proteins ATF6α and ATF6β are regulatory proteins which belong to the bZIP transcription factor family. ATF6 binds to the ER membrane via its hydrophobic sequence. The ATF6 activation process during ER stress is different from the PERK and IRE1 activation processes. After GRP78 releases from ATF6, it translocates to the Golgi apparatus from the ER and the site1 and site2 proteases splice the ATF6s juxtamembrane site. After that, ATF6 translocates to the nucleus as a transcription factor for gene expression regulation. ATF6 stimulates homodimerization or heterodimerization of the ER stress related genes such as XBP1, IRE1, PDI, α-mannosidase-like protein 1 (EDEM1) as a result of misfolded protein degradation. In the literature it has been not clarified yet whether AFF6 regulates calcineurin 1 (RCAN1) which has calcium dependent pro-apoptotic functions [44, 45].

RCAN1's important substrates are pro-apoptotic Bcl-2 family members and Bcl-2 antagonist of cell death (BAD). Calcineurin dephosphorylates BAD and in turn

BAD dimerizes with the anti-apoptotic protein Bcl-Xl and inhibits its function. Cyclic AMP responsive element binding proteins such as CREB3l1 (oasis), CREB3l2, CREB3 (luman), CREB4, CREB-H are the other known ER stress transcription factors, however their mechanisms are not yet well detailed [46].

4. Endoplasmic reticulum stress mediator proteins

4.1 CHOP

C/EBP homologous protein (CHOP or DDIT3 or GADD153) is a bZIP transcription factor that regulates IRE1, PERK and ATF6 under ER stress conditions. ATF4, ATF6 and XBP1, important elements of UPR signaling, can bind to the CHOP gene promoter sequences to regulate its transcription [43, 44].

It has been demonstrated that with knock-out PERK and ATF4, CHOP induction was disrupted under ER stress, and also ATF2 and IRE1-ASK-p38 signaling pathways upregulated the activity of CHOP. CHOP induces apoptosis via inhibition of Bcl-2. CHOP and ERo1α together enhance the ER stress dependent protein loading in the cell which also enhances the apoptosis mechanism. Moreover, CHOP interacts with pro-apoptotic Bim to activate it and also inhibits Bcl-2, thus apoptosis occurs under ER stress condition. However, CHOP is not the main protein for ER stress-mediated cell death, it was demonstrated that ER stress-mediated apoptosis can occur without CHOP expression in $PERK^{-/-}$ and EIF2α (Ser51Ala) knock-in cells [27, 30, 46–48].

4.2 GADD34

GADD34 expression in the cell is associated with apoptotic cell death. As a protein phosphatase 1 (PP1)-interacting protein GADD34, dephosphorylates eIF2α which results with protein translation inhibition. The detailed mechanistic pathway which lays under GADD34-induced apoptosis has not been clarified yet. GADD34 expression may increase the pro-apoptotic proteins. It has been demonstrated in studies that blocking the GADD34 pathway in the cell can cause inhibition of R-stress-mediated apoptosis [5, 24].

4.3 BCL-2 proteins, calcium and caspases

Bcl2 family members are regulatory proteins of apoptosis which especially modulate the mitochondrial apoptotic pathway. In resting cells, on the mitochondria and ER membrane, the Bcl2 protein interacts with the pro-apoptotic proteins Bax and Bak and inhibits their functions. Moreover, dynein interacts with the pro-apoptotic protein Bim and inhibits its function. ER stress affects mitochondria and follows the same mechanism of the mitochondrial apoptotic pathway. During prolonged ER stress after activation of CHOP and JNK, Bim phosphorylates and releases from dynein. At the same time Bax and Bak unbound from Bcl2 and the execution phase of apoptosis initiates. During ER stress-mediated apoptosis cytochrome-c releases from mitochondria and apoptosome formation occurs [49, 50].

Detailed molecular information about the ER stress modulated apoptosis mechanism needs further investigations to clarify the different genes and proteins which play role in this mechanism, thus, new generation therapy models generation can be designed for ER stress-mediated apoptosis related diseases. It has been well known that CHOP and JNK play a central role in the activation of ER stress-mediated apoptosis. Bcl2 gene expression is inhibited by CHOP, which leads to the pro-apoptotic Bcl2 family members' activation. The functions of the Bcl2 family

members also are regulated by JNK through phosphorylation. The IRE1-ASK1 pathway activates the JNK and JNK first phosphorylates the Bcl2 which is localized on the ER membrane. The BH3-only proteins on ER membrane gets activated and thus intracellular calcium flux become uncontrollable [51]. On the other hand JNK targets to BH3-only proteins are known as the "orchestrators of apoptosis." It has been reported that, the p53-upregulated modulator of apoptosis (PUMA), Noxa and Bim play roles in ER stress-mediated cell death. The Bim protein have three isoforms as short (BimS), and long (BimL and BimEL). Bim tethers dynein in the cell via its long isoforms BimL and BimEL under normal conditions, however under ER stress JNK phosphorylates Bim and stimulates its release from dynein leading to apoptosis initiation. Moreover, IRE1 induction directly activates Bax and Bak during ER stress-mediated apoptosis [52, 53].

All these activation processes are figured out with caspase activation. However, the caspase activation phase has not been defined clearly yet. It has been reported in different studies that caspases 12, 3, 6, 7, 8 and 9 do not play role in ER stress-mediated cell death. It has been speculated that caspase-4 maintains caspase-12's function in mammalians; however, it is not clarified yet [5]. It has been recently reported that in mammalians caspase-4, which is activated by ER stress, induces Bap31 and Bap20 proteins which play a role in the activation of the mitochondrial apoptotic pathway [54].

The Bcl2 family members (BCL-2 and BCL-XL) and transmembrane BAX inhibitor motif (TMBIM) (BI-1/TMBIM6 and GRINA/TMBIM3) interact and regulate IP3R activity. While cytosolic calcium level increases, BAX/BAX oligomerization (MOMP) occurs in the mitochondria and promotes the apoptotic pathway. ER foldase enzymes such as BiP and Protein disulfide isomerases (PDIs) translocate to the cytosol through BAX/BAX pores and in turn affect the plasma membrane pro-apoptotic protein Par-4 which results with apoptosis [11].

Caspase 12 and its polymorphic variant caspase 4 play an important promoting step role for ER stress-induced apoptosis. Caspase 12 activates pro-caspase-9, which belongs to the mitochondrial apoptotic pathway, without cytochrome-c release. Cytoplasmic calcium-activated protease calpain can activate caspase-12 by its cleavage and IRE1α also activates caspase-12 directly. Caspase-12 is located in the cell as a high molecular weight complex that includes apoptosis-linked gene-2 protein and p97 (ERAD mediator). P97 plays a crucial role for this pro-apoptotic stabilization of caspase-12. Once caspase-12 is activated, it activates the downstream caspases such as caspase-9 and caspase-7 which ultimately activates caspase-3; and hereby, apoptosis execution phase starts [55, 56].

5. Endoplasmic reticulum stress and autophagy

Endoplasmic reticulum (ER) stress is also closely related to the autophagy mechanism in the cell to maintain cellular homeostasis. Generation of autophagosomes occurs during the ER stress-induced autophagy process which encapsulates protein and damaged protein aggregates. As in the apoptosis process, PERK, IRE1 and ATF6 signaling pathways have role in initiating autophagy during ER stress, in addition Atg40/FAM134B takes part too [57]. Autophagy has crucial roles in maintaining optimum cellular activity, elimination of unfolded and misfolded proteins, elimination of defective organelles, protection against pathogens, balancing cellular energy storage, tumor suppression, biosynthesis of new molecules and cell death mechanisms [58].

ER stress UPR activating molecules PERK and IRE1α also activates the autophagy process by activating autophagy-related genes (Atg). Autophagosome formations generated by Atg proteins interact with the LC3II-PE complex. IRE1α-JNK pathway

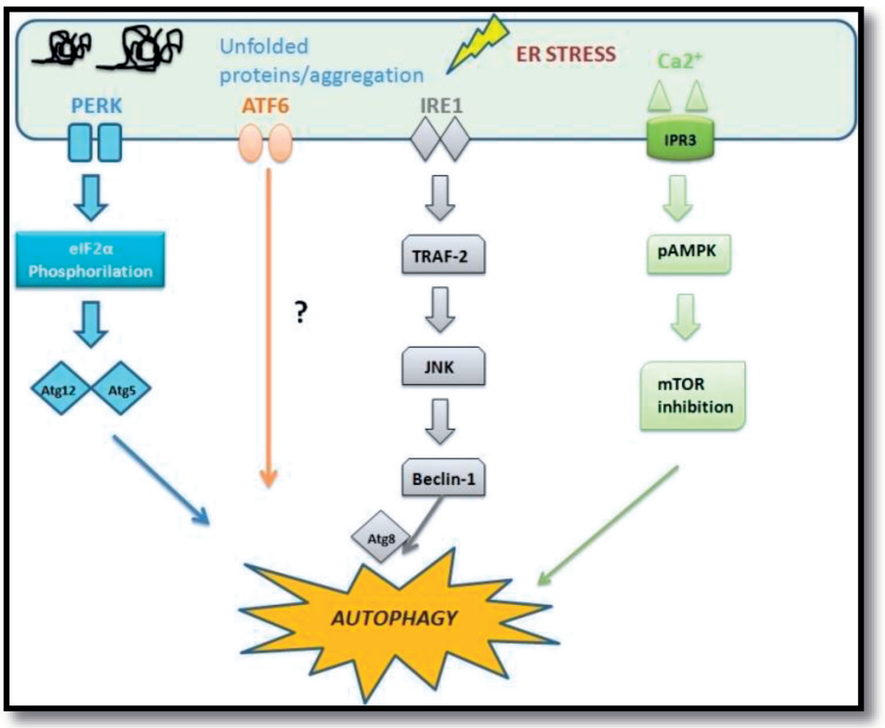

Figure 2.
ER stress-mediated autophagy induction via PERK, IRE1α, ATF6 and IPR3. PERK induce autophagy through eIF2α with Atg12 and Atg5 interaction, however ATF6 dependent pathway have not been clarified yet. Autophagy initiate by another pathway as Ca^{2+} influx through IPR3 transmembrane protein which inhibits mTOR. IRE1α pathway induce beclin-1 during autophagy induction processes.

activates Bcl2 by phosphorylation and subsequently stimulates Beclin1, ATG5 and ATG7. Thus, the Bcl2-Beclin complex dissociates and protein kinase-C activation phosphorylates LC3 and other autophagosome proteins. Another regulative process for autophagy is the mTOR pathway through AMP-dependent protein kinase (AMPK) that in turn induces the autophagy activating genes [59].

Autophagy process initiates EIF2AK3 activation which results with mTOR inhibition. Active EIF2AK3 upregulates ATF4 and subsequently SESN2, DDIT3 and DDIT4 are upregulated. These three active proteins inhibit the mTOR activity. AMPK pathway is activated via several types of metabolic stress, especially cellular energy state disorders and intracellular Ca level imbalance. AMPK pathway induces ULK1 and at the same time AMPK inhibits mTOR which has an inhibitory role on ULK1. MAPK8 and DAPK1 induction processes include formation of PtdIns3K and phosphorylation of the Bcl2-Beclin1 complex (**Figure 2**). All UPR sensory proteins have the potential to induce Beclin1 and Atg proteins for autophagy initiation. All UPR initiating molecules (IRE1, PERK, ATF4 and ATF6) activate the autophagy related protein Atg5-Atg12-Atg16 through CHOP activation. In mammalians, the ER stress-mediated autophagy mechanism is well defined and as an interesting point, under normal conditions the autophagy process plays a role for maintaining cellular homeostasis, however under stress conditions cellular mechanisms may inhibit the autophagy process with unknown regulative pathways. To understand the whole mechanism which takes part in ER stress-mediated autophagy, further studies are needed [57, 58].

6. Discussion

ER is pivotal organelle for cellular protein, lipid synthesis and Ca storage. During cell cycle process, ER is very active due to these physiological processes and addition due to its highly powerful stress response mechanism as UPR [60]. ER stress induces

several different complex molecular pathways in the cell which may conclude physiological or pathological conditions. UPR signaling mechanism is one of the important cell protective homeostasis provider factor. UPR signaling rapidly initiate with IRE1α signaling after stress stimulus, secondly ATF6 pathway become a part of activity because of its slow kinetics and finally PERK mechanism step in. UPR mechanism have balancing role between cytoprotective and proapoptotic systems. Molecular features of ER stress and UPR mechanism is crucial for delivering targeted drugs for diseases which are associated with these signaling pathways [35]. There are several ongoing studies about ER stress mechanism to clarify signaling pathways, however many unknown mechanisms about pathway remain. As discussed in this chapter different signaling mechanisms play role in ER stress-mediated cell death however; pro-apoptotic mechanism components different from PERK, CHOP, Bcl-2 family members are not identified fully yet [11, 61, 62].

The ER stress mechanism plays an important role in several different diseases such as neurodegenerative diseases, ophthalmology disorders, inflammation diseases, viral infections, cancer, metabolic diseases, and atherosclerosis. It is important to understand the detailed mechanism which plays a role in ER stress-mediated diseases to provide more effective therapeutics. Alzheimer disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), prion diseases, retinitis pigmentosa, glaucoma, macular degeneration, as inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, heart failure, cardiac hypertrophy, myocardial infraction and type I autoimmune diabetes are ER stress dependent diseases. In AD, mutant presenilin 1 interferes with the UPR mechanism and causes disruption in IRE1α, PERK and ATF6 signaling pathway and increase CHOP activity as a consequence of amyloid β-precursor protein (APP) accumulation in the neuron cells. Parkin is an important E3 ubiquitin ligase and it is also associated with ER stress-mediated cell death. The Mutant parkin gene causes accumulation of Lewy bodies in neurons that associated with defective UPR mechanism which result as Parkinson disease. ER stress mechanism depression is a very important strategy for cancer therapy. ER stress mechanism helps the tumor cells to adapt to its microenvironment. UPR plays a protective role for tumor cells and thus inhibition of ER stress could provide reducing in tumorigenesis. IRE1α/XBP1 has a crucial role in tumor angiogenesis. Considering all this together, ER stress and UPR pathways are important targets for chemotherapeutics [8, 44, 63].

7. Conclusion

ER stress-mediated cell death has a crucial role in several diseases pathophysiology. In recent years several studies have been done on the mechanism of ER stress, pathway details, its role in diseases and therapy. However, all these information are just the tips of the iceberg. To put forward effective therapeutic strategies, mechanistic pathway details should be defined well with further studies. ER stress seems to be a central mechanism to cell survival and cell death. Pathway associations with the other intracellular mechanisms are also needed to be clarified in order to understand the complexity.

Acknowledgements

The authors would like thank to Prof. Dr. Gül Özhan from Istanbul University, Faculty of Pharmacy, Department of Toxicology.

For valuable critiques and contributions, Sinem Beyaz for technical and graphical support and MSc. Ayşenur Günaydın and Pharm. Enes Bişirir for linguistic support.

This research received no specific grant from any funding agency in the public, commercial, private, or not-for-profit sectors.

Conflict of interest

The authors declare that there is no conflict of interest.

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