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Endoplasmic reticulum-mediated unfolded protein response and mitochondrial apoptosis in cancer

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Abstract

Abrogation of endoplasmic reticulum (ER) protein folding triggered by exogenous or endogenous factors, stimulates a cellular stress response, termed ER stress. ER stress reestablishes ER homeostasis through integrated signaling termed the ER-unfolded protein response (UPR^{ER}). In the presence of severe toxic or prolonged ER stress, the pro-survival function of UPR^{ER} is transformed into a lethal signal transmitted to and executed through mitochondria. Mitochondria are key for both apoptotic and autophagic cell death. Thus ER is vital in sensing and coordinating stress pathways to maintain overall physiological homeostasis. However, this function is deregulated in cancer, resulting in resistance to apoptosis induction in response to various stressors including therapeutic agents. Here we review the connections between ER stress and mitochondrial apoptosis, describing potential cancer therapeutic targets.

Keywords

mitochondria; apoptosis; autophagy; endoplasmic reticulum; unfolded protein response

1. Introduction

Coordination of external or internal cellular stress into overall stress signaling is an essential cellular process vital for cell growth and survival during organism development. The endoplasmic reticulum (ER) is a central eukaryotic cellular organelle that provides crucial biosynthetic, stress-sensing, and signaling functions [1, 2]. In addition to its role in folding and posttranslational modifications of proteins that are destined for the secretory pathway, the ER also maintains an efficient oxidizing and Ca^{2+}-rich folding environment within cells [3–5]. ER-resident chaperones, such as calnexin, calreticulin, the glucose-regulated protein GRP78 (HSPA5, also called BiP), and protein disulfide isomerases, are involved in protein

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folding, signal transduction, and maintenance of Ca^{2+} buffering [6–10]. Pathophysiological conditions, including hypoxia, ER Ca^{2+} depletion, oxidative injury, hypoglycemia, and viral infections, affect ER homeostasis and hinder protein folding processes [11–15]. These activities ultimately result in an imbalance between protein folding load/capacity and the physiological condition is known as “ER stress.” ER stress initiates a stress response via a well-coordinated and integrated signal transduction pathway, called the unfolded protein response (UPR) [6, 11, 16–19], which primarily re-establishes ER homeostasis by harmonizing various processes of ER-UPR (UPR^{ER}) to promote cell survival [20]. In the presence of severe and irreparable ER stress, a switch in UPR^{ER} from a pro-survival mode towards a pro-death response occurs through mitochondrial engagement, leading to the activation of the intrinsic apoptosis pathway [17, 21–26]. Autophagy, another mode of inducing cell death, can also be activated in response to such unresolved stress, maintaining cellular integrity under ER stress [27–30].

Mitochondria play pivotal role in the cellular processes of bioenergetics and apoptosis [31, 32]. In the intrinsic apoptosis pathway, a signaling platform containing oligomers of the BCL2 family proteins BAX or BAK assembles on the mitochondrion to induce mitochondrial outer membrane permeabilization (MOMP), leading to release of apoptogenic factors, including cytochrome c and Smac/DIABLO, ultimately triggering apoptosis [33, 34]. The assembly of this platform is influenced by the dynamic behavior of the mitochondria and *vice versa,* ultimately regulating initiation of the cell death process. Such dynamic mitochondrial behavior is dependent on mitochondrial division (i.e., fission) and fusion processes that determine cellular characteristics including morphology and cellular distribution [35, 36]. In turn, these changes modulate overall cellular physiology by impacting cellular bioenergetics as well as the apoptosis potential in response to stress [37].

Mitochondrial division and fusion events have been linked with the ultimate cellular stress response, which is cell death [38]. Furthermore, the ER actively participates in mitochondrial division (fission), suggesting a new model that links ER stress with cell death induction involving mitochondrial dynamics and apoptosis [39]. Extrinsic or intrinsic stress signals are normally processed via the ER system and result in induction of cell survival. In the case of unresolved stress signals, cross talk with the mitochondrial system results in differential processing and induction of cell death [22, 40]. Such a relationship between the ER and mitochondria in response to various stressors could be exploited for potential development of anticancer therapies that would link the stress processed in the ER with mitochondrial apoptosis. Here, we describe the different mechanisms employed by the ER system to process and resolve various stress signals and to engage the mitochondrial system for cell death induction in the case of unresolved cellular stress (Figure 1).

2. The role of ER stress and UPR^{ER} in prosurvival signaling

The ER is an essential cellular organelle involved in several processes, including protein homeostasis, stress response, survival signaling, and Ca^{2+} homeostasis [28]. The ER is responsible for protein folding and import as part of the cellular secretory machinery pathway, and this organelle functions to maintain tightly regulated oxidizing conditions and a Ca^{2+}-rich environment [6, 22, 40, 41]. These functions of ER have been attributed to ER-

resident chaperones, such as calnexin, calreticulin, BiP/GRP78, and protein disulfide isomerases, and Ca^{2+} buffering in the ER. Pathophysiological conditions, such as oxidative insult, hypoxia, Ca^{2+} depletion, hypoglycemia, ATP depletion, and viral infections affect ER homeostasis and interfere with protein folding. This triggers an imbalance between protein folding load and capacity, generating ER stress [6, 22, 40]. In response to such stress conditions, the ER induces the UPR^{ER} signaling pathway [16, 20]. The UPR^{ER} initially restores ER homeostasis by relieving stress conditions. However, when the stress conditions are too severe and cannot be reversed, the UPR^{ER} activates a cell death pathway, usually via intrinsic apoptosis, which involves the mitochondria [16, 22]. Thus, under toxic and unresolved stress conditions, UPR^{ER} alters the cell fate from a pro-survival pathway to a pro-death mechanism, eventually inducing cell death [17, 22, 40].

The UPR^{ER} is primarily mediated by three main signaling cascades, which are activated by three unique ER stress sensors: pancreatic ER kinase-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) [42]. These ER transmembrane proteins are negatively regulated and maintained in an inactive state via binding of their luminal domains to the inhibitory chaperone BiP/GRP78 [2]. Under conditions of ER stress, BiP/GRP78 inhibition is titrated downward by the accumulation of unfolded or misfolded proteins, activating ER sensors. The Ser/Thr kinase PERK phosphorylates eukaryotic initiation factor 2 alpha (EIF2α) and nuclear factor E2-related factor 2 (NRF2) under stress conditions [42]. Phosphorylation of EIF2α inhibits global translation while preferentially promoting expression of the UPR transcription factor ATF4 [43, 44]. ATF4 regulates many genes involved in ER homeostasis, including BiP/GRP78 and GRP94, the oxidative stress response, apoptosis and amino acid biosynthesis and transport [45–49]. NRF2, a cytoprotective transcription factor, is pivotal to the antioxidant response and cell survival under oxidative stress conditions. PERK-mediated phosphorylation of NRF2 leads to its dissociation from its cytosolic repressor kelch-like Ech-associated protein 1 (KEAP1). This dissociation frees NRF2 to facilitate nuclear translocation, which ultimately induces the expression of genes involved in the antioxidant stress response [50–52].

As discussed earlier, activation of UPR^{ER} is primarily an anti-apoptotic adaptive response against toxic insults like ROS, whereas sustained activation of UPR^{ER} signaling causes cell death. Therefore, induction of UPR^{ER} is an attractive strategy to target cancer cells. Many drugs have shown promising results in inducing UPR^{ER} and some of these drugs are under clinical trials [11, 53–55]. Although, these UPR^{ER} inducing drugs are not as successful as expected (Reviewed in [56] and [11]), the activation of NRF2 by PERK has been considered as one of the main reasons for the pro-survival effect of UPR^{ER}. The activation of NRF2 induces antioxidant defense system as well as upregulates the expression of BCL-2 and Bcl-xL by binding to the ARE (antioxidant response element) leading to the prevention of apoptosis [57–60]. BCL-2 and Bcl-xL are anti-apoptotic proteins and prevent the oligomerization of pro-apoptotic proteins BAX and BAK, thus blocking the release of cytochrome c from mitochondria [61–63]. Bcl-xL also interacts with apoptotic protease activating factor 1 (Apaf-1) in the cytosol and inhibits the Apaf-1 dependent activation of caspase-9 [64]. Furthermore, prolonged UPR^{ER} induces apoptosis in p53-dependent manner via p53-up-regulated modulator of apoptosis (PUMA) and NOXA, pro-apoptotic members

of Bcl-2 family proteins [65]. Thus, induction of UPR^{ER} results in the activation of the PERK-EIF2α-ATF4 and PERK-NRF2 signaling cascades, which promotes survival of ER-stressed cells by restoring ER quality control and enhancing oxidative stress adaptation along with overexpression of BCL-2 and Bcl-xL (Figure 1). These studies clearly suggest that inhibition of NRF2 along with UPR^{ER} induction is required for anti-cancer strategies.

Stimulation of IRE1, another ER-stress sensor, provides both protein kinase and endoribonuclease activity, although IRE1 itself is the only known direct substrate of this protein kinase activity. Auto phosphorylation of IRE1 is required for its endoribonuclease activity and splicing of XBP1u (u for unspliced) mRNA to yield mature XBP1s (s for spliced) mRNA, which encodes XBP1s, a potent transcription factor that induces expression of genes involved in ER quality control, ER/Golgi biogenesis, and ER-associated protein degradation (ERAD) components in addition to expression of genes involved in redox homeostasis and oxidative stress response, ultimately impacting cell fate decisions [66–68]. Finally, BiP/GRP78 dissociation activates ATF6 and induces its translocation to the Golgi apparatus. In the Golgi apparatus, proteases cleave and process ATF6 to produce an active transcription factor that regulates genes encoding ER chaperones and ERAD components and also those that play essential roles in lipid biogenesis and ER expansion [69, 70].

3. ER stress-mediated UPR^{ER} in pro-death signaling

Under tolerable stress conditions UPR^{ER} signaling induces pro-survival pathways that lead to resistance and cell survival. While, in the presence of stress conditions that are severe, highly toxic, and irreversible, the same UPR^{ER} pathway induces pro-death mechanisms [22]. Although the molecular mechanisms behind such switching are poorly understood, it has been reported that the UPR^{ER} employs some of the sensors and executioners of pro-survival mechanisms to mediate pro-death pathways in response to toxic stress levels [71, 72]. Mild ER stress results in expression of ATF4-dependent pro-survival genes as well as a transient and limited activation of PERK. During severe ER stress, sustained PERK signaling induces phosphorylation of EIF2α, which in turn increases the translation of ATF4 [71]. ATF4 is a transcription factor known to bind the promoter region and enhance C/EBP homologous protein (CHOP) mRNA expression and thus protein levels [74]. CHOP plays an important role in ER stress-induced cellular death [2], as this factor is a target gene common to all three apical ER sensors/executioners. Under severe ER stress conditions, ATF4 and CHOP interact together and induces cell death *via* induction of genes involved in protein synthesis such as GADD34 and ERO 1α. The increased protein synthesis further worsens the ER stress load and leads to ATP depletion and oxidative stress resulting in a hyper-oxidizing ER environment [71]. Another, pro-survival IRE1-XBP1 signaling that exists under mild stress conditions is counterbalanced by IRE1 scaffold-signaling properties that are independent of its XBP1 splicing activity. IRE1 serves as a molecular platform to recruit the E3 ubiquitin ligase adaptor protein TNF receptor-associated factor 2 (TRAF2), and this factor then tethers IRE1 to the stress-activated ASK1-JNK/p38 MAPK cascade, which functions in cell fate decisions [20]. Both of these mechanisms lead to severe unresolved ER stress, ultimately resulting in apoptosis due to ER collapse [50, 76]. Thus, it is very clear that the ER stress response duality may be mediated by the differential stability of mRNA/protein factors under different levels of stress conditions [73] and the transition of UPR^{ER} from pro-survival

to pro-apoptotic effects depends on sustained PERK and IRE1 signaling [75]. Furthermore, CHOP regulates BCL2 family protein expression, which regulates the intrinsic apoptosis pathway. Thus, ER stress-induced UPR^{ER} links mitochondrial apoptosis with ER stress by modulation of the intrinsic apoptosis cascade, and this cross talk alleviates any unresolved ER stress via induction of cell death [78–80].

In addition to such cross talk between the UPR^{ER} and the intrinsic apoptotic pathway, cleavage and subsequent activation of ER-associated caspases, including caspase 12, during ER stress induces apoptosis in response to ER stress [81, 82]. Caspase-12 in rodents and caspase-4 in humans induce apoptosis in response to ER stress, typically in a CHOP-dependent manner [83, 84]. Regulation of Ca^{2+} homeostasis is another mechanism that modulates the mitochondrial apoptosis pathway via ER dynamics. Cleavage of the ER transmembrane protein BAP31 by ER-associated casapase-8 generates the p20 fragment, and abrogates the prosurvival functions of BAP31 [85]. In addition, p20, a caspase-8 cleavage fragment of BAP31 stimulates Ca^{2+} release from ER into the cytosol, resulting in mitochondrial uptake of Ca^{2+}, fission, and cytochrome c release, all of which induce apoptosis (Figure 2). Anticancer agents, such as alkyl-lysophospholipid and edelfosine, have commandeered this mechanism to induce apoptosis following ER stress [86]. In addition, early cleavage of BAP31 by caspase-8 in anthracyclines-induced ER stress results in calreticulin mobilization from ER lumen to the plasma membrane, and this confers immunogenic properties to the apoptosis process [87].

4. UPR^{ER}-mediated autophagy

Macro-autophagy (or autophagy), a lysosomal degradation pathway for proteins and organelles, is essential for normal cellular homeostasis and serves as a major housekeeping mechanism in eukaryotic cells. In addition, autophagy is another cellular mechanism that can be employed to cope with ER stress [20, 30, 88]. The role of autophagy in ER stress is not completely understood; however, an overload of ER-resident unfolded proteins combined with an insufficient proteasome-mediated degradation system, resulting in persistence of the damage/stress, is thought to trigger autophagy to alleviate the ER stress, serving as an ER protein quality control system [27]. Autophagy induction exerts a pro-survival function by alleviating ER stress induced by multiple stressors [27, 88]. For example, activation of the ER-stress associated transcription factor CHOP induces the autophagy gene transcriptional program, which ultimately leads to autophagosome formation and autophagy (Figure 3). Essentially, autophagy ameliorates ER stress by removing aggregates or toxic proteins that were not removed by conventional proteasome-mediated degradation [89]. ER stress is often associated with Ca^{2+} release into the cytosol, and this increase in cytosolic Ca^{2+} levels activates regulatory pathways for both autophagy and apoptosis [90–92]. ER stress-mediated activation of autophagy is linked to increased adaptation and cell survival in response to physiological/pathological stress conditions [30, 88, 93, 94]; however, as in UPR^{ER}, autophagy also induce cell death via either enhancing apoptotic or non-apoptotic pathways during the ER stress response [93, 95, 96]. Importantly, since conventional apoptotic pathways are highly deregulated in cancer, cell death induction via autophagy is a seemingly attractive and promising option for killing of tumor cells.

5. Cross talk between UPR^{ER} and mitochondrial apoptosis

Stress-induced changes in ER physiology and the concomitant UPR^{ER} lead to modulation of mitochondrial function and ultimately to apoptosis in response to unresolved stress. This cross talk plays an important role in overall cellular physiology via involvement of mitochondrial apoptosis. Thus, cross-talk dynamics decide cell fate with respect to survival or death following ER stress. In addition to modulating ER stress-induced cell death, CHOP also regulates BCL2 protein family member expression [97, 98]. Although BCL2 family proteins directly regulate the intrinsic apoptotic pathway, these proteins also function as regulators of ER homeostasis through their participation in UPR^{ER} sensor mechanisms and cell fate decisions following ER stress [78].

The complex dynamic interplay between UPR^{ER} components and BCL2 family members determines cell fate following ER stress. In fact, the physical interaction between UPR^{ER} sensors and BCL2 family members appears to modulate ER stress-mediated activation of the intrinsic apoptosis pathway. Specifically, the pro-apoptotic proteins BAX and BAK not only regulate the Ca^{2+} levels in the ER but also modulate the activity of the UPR^{ER} sensor IRE1 via physical interaction, thus performing essential roles in the induction of mitochondrial apoptosis following ER stress-induced UPR^{ER} [78]. While BCL2 proteins can modulate IRE1 activity, IRE1 self-activation also activates the MAPK/JNK pathway, which in turn, activates BH3-only proteins, including BIM, and suppresses the anti-apoptotic activity of BCL2 [99, 100]. Augmenting this effect, CHOP induces BIM transcription while simultaneously suppressing BCL-2 induction, linking the ER stress response to mitochondrial apoptosis [97, 98, 101]. In addition, other BH3-only proteins, such as NOXA and PUMA, are also transcriptionally activated following ER stress, and such activation can occur in either a p53-dependent or -independent manner [65, 102–104].

Activation of the IRE1-TRAF2 signaling pathway appears to be important for linking ER stress to mitochondrial apoptosis. In BAX/BAK-deficient murine epidermal fibroblasts, reconstitution of BAK expression at the ER membrane reactivated IRE1-TRAF2 signaling as well as mitochondrial apoptosis mediated by reticular forms of BIM and PUMA, precluding the need for a mitochondrial localization event [105]. These events are vital for a rapid response following unresolved ER stress, and circumventing the need for mitochondrial localization for these proteins removes another possible regulatory step in apoptosis induction in response to ER stress. Furthermore, mobilization of Ca^{2+} promotes persistent JNK activation and mitochondrial apoptosis exclusively in an atypical IRE1-TRAF2 activation pathway that is dependent on ER BAK [105]. JNK is involved in regulation of both apoptotic and autophagic cell death pathways following ER stress; therefore, activation of the JNK pathway connects ER stress to mitochondrial apoptosis via UPR^{ER} [106]. These findings offer insight into the complex cross talk between ER stress and cell fate decisions via UPR. In many diseases, including cancer, this cross talk is deregulated and therefore offers an exciting target for intervention and treatment development [107]. Thus, manipulation of ER stress in such a way as to induce apoptosis through the mitochondrial pathway provides a desirable option for inducing cell death in otherwise resistant cancer cells. Agents that mediate such cross talk between ER stress and

the intrinsic cell death pathway would likely rely on engaging the UPR^{ER} with the IRE1-TRAF2 circuit.

6. The role of ER in mitochondrial dynamics

Mitochondria were incorporated into the eukaryotic system early during evolution, and this event enabled these organisms to overcome the steep energetic barrier involved in continuous production of ATP [31]. This incorporated endosymbiont amplified the essential feature of eukaryotic programmed cell death, or apoptosis. During mitochondrial (intrinsic) apoptosis, a signaling platform is recruited for assembly on the mitochondria, leading to permeabilization of the outer mitochondrial membrane and release of apoptogenic proteins into the cytosol [33, 34]. Dramatic changes including fission and fusion processes in mitochondria influence cell death, determine the overall shape, connectedness, and distribution of mitochondria in cells. The ER influences mitochondrial dynamics and thus, links the cell's physiological state with mitochondrial apoptosis [38]. Cross-talk between the ER and mitochondria ensures that cellular physiology is tightly regulated and that adequate responses to stress signals are initiated to avoid toxic physiological damage. In addition to connecting stress signals to the mitochondria via UPR^{ER}, the ER also participates in the division of mitochondria, leading to dynamic cellular changes affecting multiple cellular pathways, including those responsible for cell death [36, 38]. This new physiological concept links the ER with mitochondrial dynamics and cell death, ensuring coherence in cellular functioning in response to stress signals.

Large self-assembling dynamin-related guanosine triphosphatases (DRPs) regulate mitochondrial fission and fusion processes [35]. A single cytosolic DRP, termed DRP1, catalyzes mitochondria fission, while fusion requires the outer mitochondrial membrane proteins MFN1/MFN2 and the inner mitochondrial membrane protein OPA1. The self-assembling properties of DRP mediate the fission and fusion processes of mitochondria [108, 109]. In addition to these roles in fission and fusion, DRPs also function in pathways related to quality control and stress and affect BCL2-dependent MOMP, suggesting that DRPs directly link these processes with apoptosis in cells, although the mechanism of such modulation remains unclear. OPA1 negatively modulates MOMP through regulation of junctions near the mouths of cristae that regulate the release of apoptogenic factors from the intermembrane space [110, 111]. However, DRP1 recruitment to mitochondria modulates MOMP in a context-dependent manner. Massive recruitment and assembly of DRP1 into foci on the outer mitochondrial membrane occurs during apoptosis, resulting in fission and consequent dramatic fragmentation of the mitochondrial network. DRP1 behavior is thus similar to pro-apoptotic BAX, which is recruited to the outer mitochondrial membrane during apoptosis and oligomerizes into foci that are functionally linked to MOMP. Indeed, DRP1 has been found in foci with BAX on mitochondria during apoptosis [112–114], however, DRP1-mediated cell death may not necessarily require BAX and BAK in other cell types [115, 116]. MFN2 similarly behaves like DRP1 under apoptotic conditions and has been found in foci with BAX [112, 117]. Although these apoptotic foci mark the sites of mitochondrial fission, the role of DRP1 in modulating MOMP is independent of its role in the fission process.

Direct involvement of ER with mitochondrial apoptosis can be attributed to the formation of ER-mitochondrial microdomains [38]. These microdomains are generated via ER-associated mitochondrial division (ERMD) and can be harnessed for diverse cellular functions, including apoptosis induction under unresolved stress conditions. During ERMD, the ER associates with mitochondria and marks the sites of division [36, 118]. These microdomains are enriched for mitochondrial division components, such as DRP1 and the DRP1 receptor and effector MFF. However, under conditions of unresolved stress, these microdomains can recruit pro-apoptotic BCL2 proteins, such as BAX, and regulate their activation to promote MOMP and subsequent release of apoptogenic factors, including cytochrome c, and then cell death via apoptosis [38].

ERMD sites that demarcate the ER-mitochondria microdomains are important for BAX insertion and oligomerization. In the absence of DRP1 due to recruitment to mitochondrial constriction sites, MFF accumulates at ER-mitochondrial contact sites [36]. A proposed role for mitochondria-associated membranes in BAX activation stems from the observation that sphingolipid metabolites from a non-mitochondrial membrane compartment directly promote the assembly and oligomerization of BAX in the mitochondrial outer membrane to induce MOMP [119]. In a similar manner, these ER-mitochondrial microdomains may facilitate the shuttling of key lipid effectors of BAX as a result of the ERMD process. Overall, ERMD appears to be a critical process in dynamic cellular physiology, linking the ER and mitochondria and mediating apoptosis via MOMP induction in response to unresolved ER stress. It is possible, however, that ERMD domains extend beyond the contact sites into the lumens of both the ER and mitochondria, thereby integrating the functional status of these organelles. Notably, ER-mitochondria contacts via formation of ERMD domains are not only responsible for normal cellular physiology, mediating mitochondrial fission/fusion or cell death, but may also be involved in pathologies, including cancer [120–122]. Therefore, ER-mitochondria interaction has important clinical relevance and offers an opportunity for therapeutic exploitation in oncology. Agents that induce unresolved stress conditions and also stimulate ERMD microdomain-induced MOMP and cell death would be highly desirable for cancer therapy, as suggested by the regulation of MOMP via ER stress-induced apoptosis. Moreover, mitochondrial dysfunction and ER stress have been implicated in diseases that have been associated with altered mitochondrial dynamics, such as neurodegeneration [120, 121].

7. Conclusions and future perspectives

The ER is one of the central organelles involved in the maintenance of cellular homeostasis. Disruption or malfunctioning of the ER due to ER stress has been associated with multiple pathological conditions, including cancer. This deregulation of ER function underlies the pro-apoptotic mechanism of various anticancer regimens; however, ER stress-induced signaling pathways and their molecular mechanisms are quite complex and have dual functions in cell survival and death (Figure 1). The ER and mitochondria communicate with each other to maintain normal physiological homeostasis at a steady-state level. Their individual and coordinated functions are essential for maintaining quality control and the overall physiological state of eukaryotic cellular systems (Figure 1). Disruption of this association commonly occurs in various malignancies and leads to pro-tumorigenic events,

such as apoptosis resistance, which is an important hallmark of cancer. Elucidating the mechanisms of signaling by the ER stress pathways in order to promote cell death or cell survival induction comprises a major focus in the field and will provide an important aspect of rational drug design for therapeutic applications against diverse diseases, including cancer. Indeed, our recent findings demonstrate that activation of UPR including mitochondrial UPR plays critical role during anticancer induced apoptosis in cancer cells [123, 124], suggesting that targeting UPR may provide novel strategies for cancer therapeutics. In this regard, one possibility is the development of small molecule modulators of the kinase components of the UPR^{ER}, such as PERK and IRE1. A better mechanistic understanding of ER stress-induced intrinsic apoptosis via the UPR^{ER} demands immediate attention and could pave the way for rational design of UPR^{ER}-based anticancer drugs. One potential challenge will be the development of agents that specifically target the cyto-protective functions of the UPR^{ER} while either potentiating or maintaining the pro-apoptotic functions of this response. Promising agents [95, 125–136] are under investigation in various types of cancer, and possible combination therapies utilizing ER stress-inducing agents are encouraging approaches (Table 1). In conclusion, UPR^{ER}-mediated induction of the mitochondrial intrinsic apoptosis pathway in response to anticancer targeting is an attractive strategy for novel cancer therapy investigations and thus offers considerable potential for future drug design for the treatment of various malignancies.

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Highlights

- UPR^{ER} promotes switch from pro-survival to pro-death signaling under severe stress.
- Mitochondria facilitate pro-death signaling initiated by UPR^{ER}.
- ER-mediated mitochondrial dynamics affect mitochondrial function.
- Deregulated UPR^{ER}-mitochondrial crosstalk confers resistance to apoptosis.
- Promoting UPR^{ER} pro-death signaling is an intriguing strategy for cancer therapy.

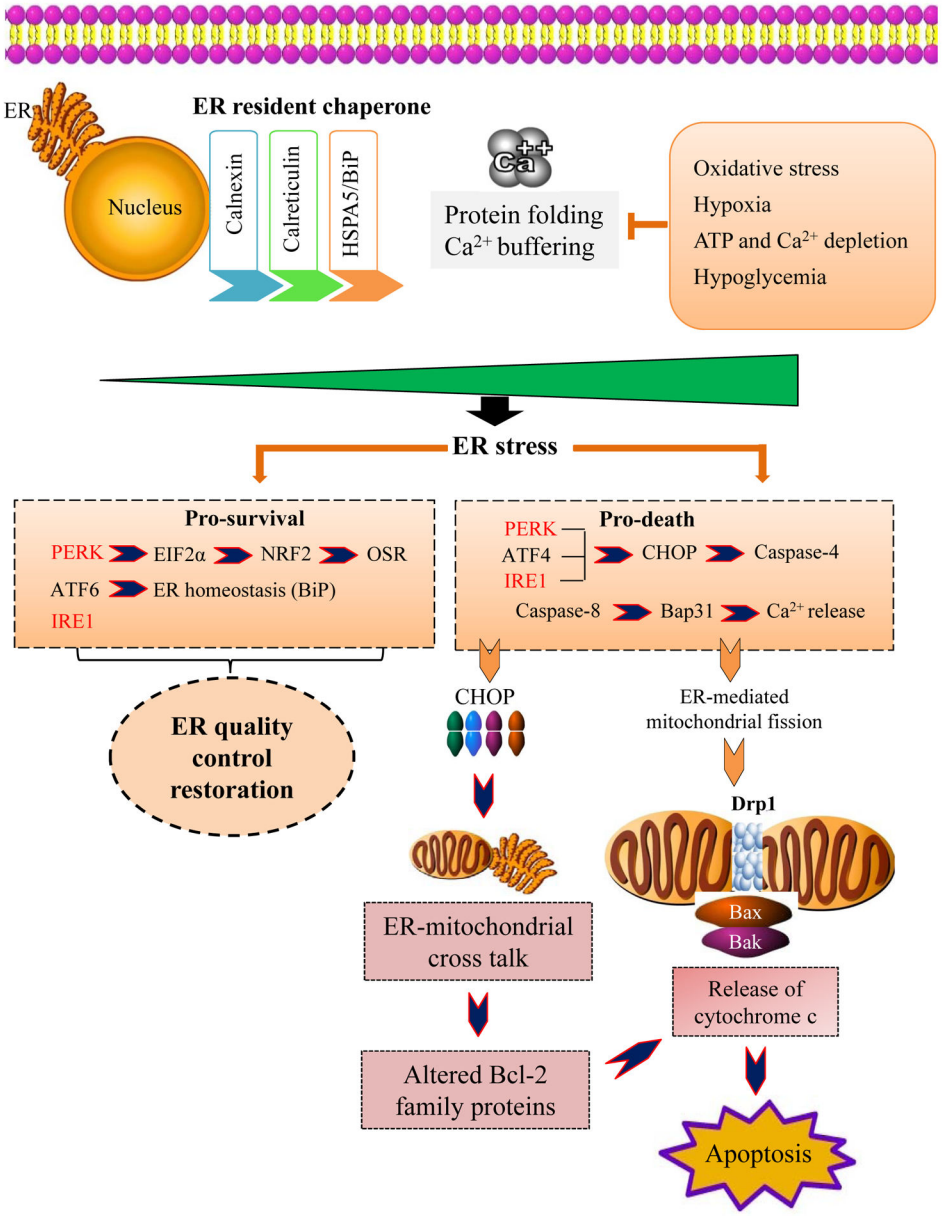

Figure 1.

A schematic representation of ER-mitochondrial crosstalk. The UPR^{ER} is initiated by ER stress, which modulates ER function and stimulates mitochondrial-mediated intrinsic apoptosis *via* crosstalk with mitochondria and nucleus. See text for details. OSR, oxidative stress response

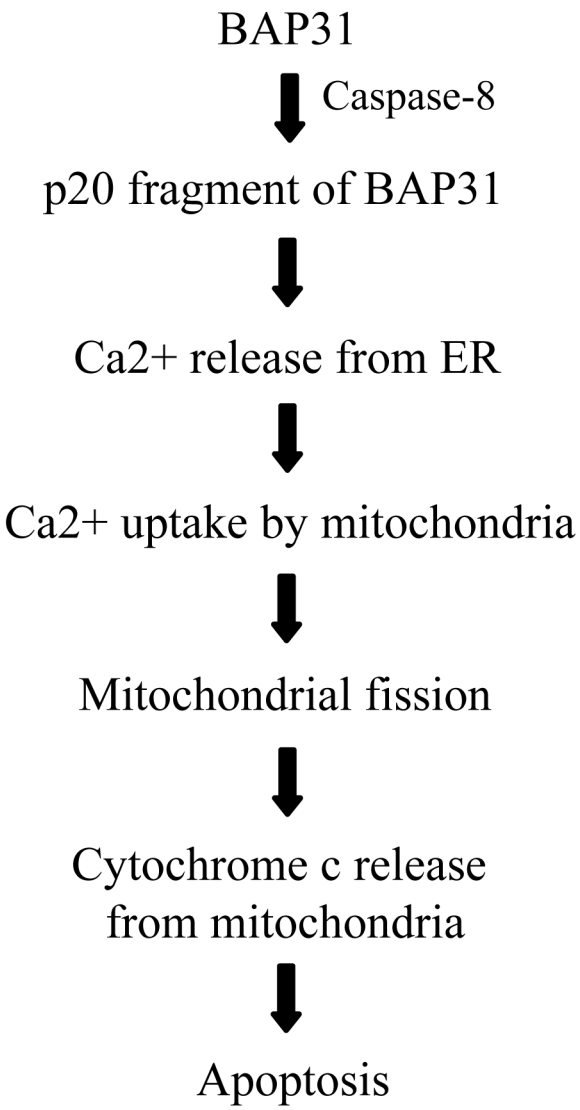

Figure 2.

The role of calcium in ER-mitochondrial crosstalk. Caspase-8 cleaved fragment of BAP31 stimulates Ca^{2+} release from the ER into the cytosol. This is followed by mitochondrial uptake of Ca^{2+}, leading to mitochondrial fission, enhancement of cytochrome c release, and apoptosis.

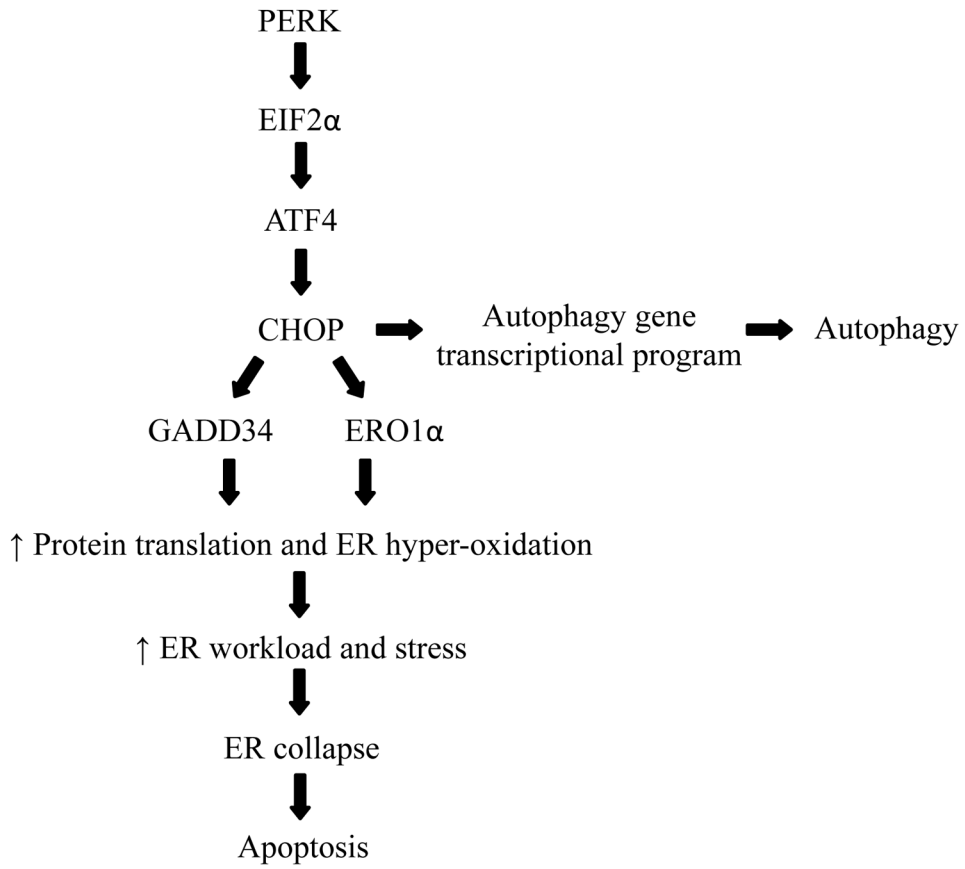

Figure 3.

Role of PERK signaling in cell death. Sustained PERK signaling activates EIF2α, and in turn increases the translation of ATF4, which then targets transcription factor CHOP. CHOP can either activate autophagy program or induce GADD34 and ERO1α to promote hyperoxidizing ER environment, which further increases ER stress, leading to ER collapse and apoptosis.

Table 1

ER stress-inducing agents in cancer.

Agents	Cancer type	Mechanism of action	References
Resveratrol (RSV)	Prostate cancer	RSV triggers ER stress by depleting ER Ca^{2+} pool and induces autophagy-mediated apoptosis.	Selvaraj et al., 2016
Withaferin A	Renal carcinoma	Withaferin A induces apoptosis in human renal carcinoma cells via ER stress.	Choi et al., 2011
Withaferin A	Pancreatic cancer	Withaferin A causes impaired autophagy and ER stress-mediated apoptosis in pancreatic cancer cells.	Li et al., 2016
β-phenethyl isothiocyanate (PEITC)	Ovarian cancer	PEITC promotes ROS accumulation and UPR- mediated apoptosis in ovarian cancer cells	Hong et al., 2015
Silibinin	Prostate cancer	Silibinin induces ER stress in prostate cancer cells by inducing ROS generation.	Kim et al., 2016
Subtilase cytotoxin AB (SubAB)	Colon cancer	ER stress induces cancer stem cell differentiation and sensitizes cells to traditional chemotherapy.	Wielenga et al., 2015
Sulforaphane (SFN)	Prostate cancer	SFN induces ROS generation and initiates apoptosis.	Singh et al., 2005
Delta(9)- tetrahydrocannabinol (THC)	Glioblastoma	THC induces ER stress via ceramide accumulation within the ER, which increases phosphorylation of eIf2alpha, ATF4 and CHOP upregulation, and promotes autophagy and apoptosis in cancer cells.	Salazar et al, 2009
Cantharidin (CTD)	Lung Cancer	CTD induces ROS and Ca^{2+} production. ER-stress induced proteins associates with a decrease in mitochondrial membrane potential. Cells treated with CTD ultimately undergo apoptosis.	Hsia et al, 2014.
Bortezomib (BTZ)	Cholangiocarcinoma	BTZ induces ER-UPR and subsequently activates intrinsic apoptosis.	Vaeteewoottacharn et al., 2013
GSK 2656157	Pancreatic cancer	Induction of ER stress via inhibition of PERK decreases tumor size and vascularization *in vivo.*	Atkins et al., 2013
Versipelostatin (VSL)	Stomach cancer, colon cancer, and fibrosarcoma	VSL inhibits transcription of ER-UPR gene GRP78, which in turn allows for selective killing of glucose- deprived cancer cells.	Park et al, 2004
Tunicamycin (Tm)	Breast cancer	Tm activates ER-UPR in breast cancer stem cells (CSCs), thereby decreasing the subpopulation of CSCs as well as CSC invasiveness.	Nami et al., 2016