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Mechanisms of Endoplasmic Reticulum Stress-Mediated Pathways to Apoptosis: Significance for Tumor therapy

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Abstract

The endoplasmic reticulum (ER) acts as a quality control organelle for protein homeostasis. The systems for controlling protein quality include ER-associated degradation, protein chaperones, and autophagy. Disruptions in ER function, a process called ER stress, trigger the unfolded protein response (UPR), a tightly orchestrated series of intracellular signal transduction reactions to restore protein homeostasis. The imbalance between the rate of mRNA translation and the efficiency of protein folding leads to the accumulation of unfolded or misfolded proteins inside the ER lumen which triggers ER stress. UPR is characterized by the action of three signaling proteins: inositol-required protein-1α (IRE1α), protein kinase RNA (PKR)-like ER kinase (PERK), and activating transcription factor 6 (ATF6). The persistence of chronic ER stress and protein load exceeds the ER's capacity, leading to cellular dysfunction and cell death. Accumulating evidence implicates ER stress-induced cellular dysfunction and cell death as major contributing factor to diseases such as tumors, making modulators of ER stress pathways potentially attractive targets for drug discovery. In this review we focus on the mechanisms of stress-induced pathways to apoptosis and their impact as therapeutic target in cancer treatment.

Keywords: ER, UPR, IRE1α, PERK, ATF6

Introduction

Although recent advances in tumor diagnosis and therapy have improved overall survival in cancer patients, cancer-related mortality remains to be the second cause of death worldwide (1, 2). As mentioned above, the development of cancer is due to the disruption of normal cellular functions through multi-step mechanisms mediated by various genetic and epigenetic alterations in normal cells. (3, 4). Once tumor development has been initiated, tumor cells begin to adapt to their environment through mechanisms mediated by interactions between tumor cells and cellular and non-cellular components of their microenvironment. (5, 6). As a result, uncontrolled tumor cell growth and significant dysregulation of cell death machinery occurs (7, 8). Tumor cell fate is regulated by extra- and intra cellular signaling-dependent mechanisms (9, 10). These mechanisms are tightly regulated by two main pathways, the intrinsic pathway and extrinsic pathways (11, 12). The intrinsic pathway mediates apoptosis *via* mitochondria-dependent mechanisms, whereas the extrinsic pathway mediates apoptosis *via* death

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receptor-dependent mechanisms (13). In addition to the significant role of both intrinsic and extrinsic pathways in the regulation of apoptosis, the involvement of endoplasmic reticulum (ER)-dependent mechanisms has been investigated (14-16). ER is a cellular organelle that acts as quality control for protein production, allowing only functional proteins to leave their vesicles (17, 18). The main function of ER protein quality control systems is to maintain the homeostasis of proteins, including chaperones, ATPases, glucose-regulated protein 94 (Grp94), binding immunoglobulin protein (Bip), Hsp70 family members, and proteolytic systems such as the ubiquitin-proteasome and the lysosome-autophagy (19, 20). In this review, we focus on the mechanisms of ER stress-mediated pathways to apoptosis and their impact as therapeutic targets on cancer treatment.

Endoplasmic reticulum structure, function and dysregulation

The ER is a membranous network of elongated tubes and flattened discs spanning the greatest part of the cytoplasm (21, 22). This membranous network encloses the ER lumen that serves to transfer molecules from and to the cytoplasm (23). In addition to its function as a protein synthesis factory, the ER is responsible for the storage of calcium and regulation of calcium release, synthesis and storage of lipids, and glucose metabolism (25). The different functions of the ER are carried out by different regions consisting of tubules, sheets, and the nuclear envelope (24, 25). Numerous identified proteins have been described due to their contribution to the overall architecture and dynamics of the ER (26, 27). In short, the ER is a multi-task organelle that is tightly regulated to perform many specific functions (24, 27).

Although numerous chaperones and folding enzymes are present in abundance, unfolded or misfolded proteins often accumulate in the lumen of the ER leading to ER stress (28, 29). As soon as the cell underlies this type of stress, some cellular modifications are required to maintain ER balance and proper function. The most common modifications include the inhibition of translation and degradation of unfolded or misfolded proteins, which leads to significant increase of chaperon production and folding enzymes (30, 31). Accordingly, the failure of the ER to restore balance can lead to apoptosis (32, 33). The functional structure of the endoplasmic reticulum is outlined in detail (Fig.1).

Endoplasmic reticulum stress-induced unfolded protein response-dependent pathways

UPR is initiated and regulated by the ER stress response and is mediated through three sensors located at the ER membrane: serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1α (IRE1α), activating transcription factor 6 (ATF6), and the protein Kinase RNA-Like ER Kinase (PERK) (34, 35). The release of UPR is attributed to competition between unfolded proteins with the immunoglobulin protein (BiP)-binding receptor, leading to the activation of IRE1α, ATF6, and PERK *via* BiP dissociation (34, 36). The target genes of the UPR are mostly associated with protein folding, ER-associated degradation (ERAD), oxidative stress, autophagy, mitochondrial and metabolic pathway dysregulation, and their induction both variable and tissue specific (37, 38). Binding of the unfolded protein to PERK leads to its conformational changes, which in turn facilitate the auto-multimerization and auto-phosphorylation of PERK (39, 40). Inactivation of eIF2α, the ubiquitous translation initiation factor, results from PERK activation and reduces protein synthesis and load (41, 42). Thus, sustained ER stress is required to trigger ATF4 mRNA translation and activate the C/EBP homologous protein (CHOP) promoter (42, 43).

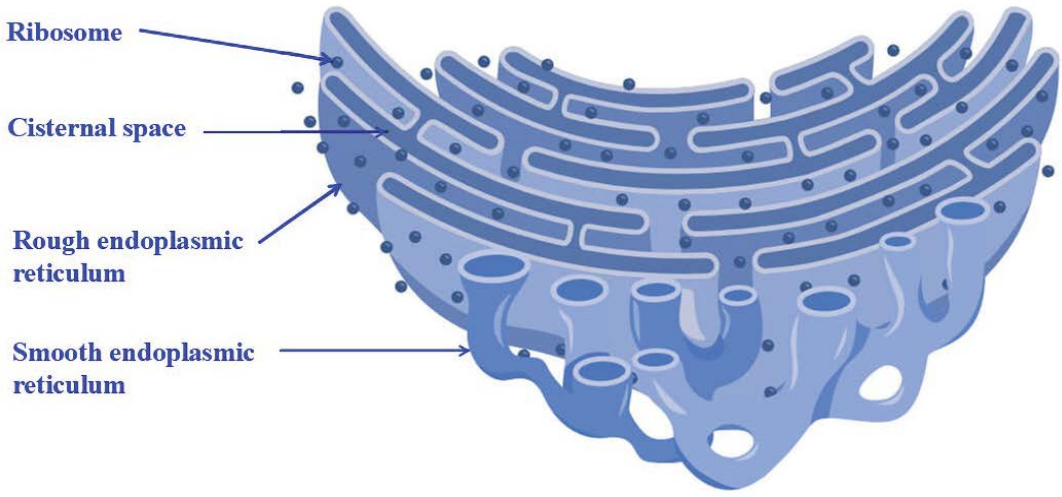

Figure 1: Functional structure of the endoplasmic reticulum

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IRE1 is a single-spanning transmembrane protein with dual protein kinase and ribonuclease activity. Once IRE1 has been activated, it dimerizes and/or oligomerizes to trigger the transphosphorylation of positive regulatory sites within the IRE1, whose phosphorylation requires adenosine nucleotides (ATP/ADP) as cofactors to exhibit nuclease activity (36, 44-46). Once nuclease activation is complete, IRE1 excises an intron (a 26-nucleotide segment) from the mRNA encoding a UPR-specific transcription factor, X-box binding protein 1 (XBP1), to convert unspliced XBP1 (XBP1u) into spliced XBP1 (XBP1s) (47, 48). ATF6 is a 90-kDa protein that is constitutively expressed in cells and is a membrane-bound transcription factor that activates genes in the ER stress response (49, 50). After accumulation of unfolded protein in the ER, ATF6 is cleaved to release its cytoplasmic domain and enters the cell nucleus (51, 52). The processing of ATF6 cleavage is mediated by both site-1 and site-2 proteases (53). Of note, ATF6 is characterized by its cytosolic NH2-terminal domain that can act as a transcription factor of the basic-leucine-zipper (bZip) family (54-56). The downstream effects of ER stress are mediated by UPR-induced protective and pro-apoptotic pathways (19, 57). Under stress conditions misfolded proteins can be removed from the folding apparatus by translocating from the ER to the cytosol (58, 59). In the cytosol the degradation of the misfolded protein is regulated by the cellular ubiquitin-proteasome system through ERAD (60, 61). The sustained accumulation of misfolded proteins in the lumen of the ER is the main cause for stress leading to the generation of an adaptive response (UPR) (62, 63). Consequently, ER stress-induced UPR results in the inhibition of protein synthesis, dysregulation of gene expression, and induction of cell death (16, 64). The mechanisms regulating the removal of misfolded protein are outlined in Figure 2

ERAD is a part of an ER-mediated protein quality control system responsible for restoring protein conformation and eliminating abnormal proteins on the ER membrane or in the cytoplasm (65, 66). The ERAD degradation mechanism is mediated by a process involving substrate recognition by chaperones and lectin, VCP/p97-directed dislocation across the ER membrane, polyubiquitination by E3 ligases, and degradation by the 26S proteasome (26, 67). The different proteasome degradation ERAD substrates include ERAD-L, ERAD-M, and ERAD-C proteins with folding problems or degradation signals located in the ER lumen, transmembrane, or cytoplasmic domain (68, 69). ERAD can attenuate ER stress induced or inhibited by UPR-dependent mechanisms (31, 70). Prolonged UPR has been reported to impair protein synthesis and exacerbate ERAD (30, 71). Furthermore, ER stress can modulate eIF2α phosphorylation, leading to attenuation of protein synthesis, while subsequent activation of ATF4/CHOP can increase protein synthesis and trigger apoptosis (72, 73). CHOP encodes a regulatory subunit of

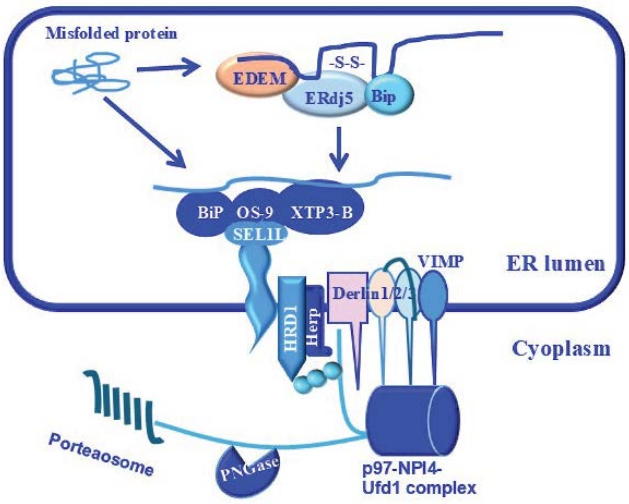

Figure 2: Endoplasmic reticulum (ER) luminal misfolded proteins are recognized by machinery including ER chaperone BiP, DnaJ family ERdj5, and lectins such as ER degradation enhancing alpha-mannosidase-like protein (EDEM) family members, OS-9, and XTP3-B. Following its recognition, the terminally misfolded protein is recruited to the HRD1 complex *via* binding with SEL1L and is brought to a putative retrotranslocon channel, which may include derlin family proteins, HRD1, or the Sec 61 complex. The protein is finally dislocated from the ER to the cytosol. Cytoplasm-exposed substrates are ubiquitinated by E3 ubiquitin ligase HRD1 and extracted by the p97-Npl4-Ufd1 complex anchored on the ER transmembrane through VIMP in an ATP-dependent manner. The extracted substrate is deglycosylated by PNGase, deubiquitinated, and degraded by the proteasome.

an eIF2α-mediated phosphatase complex that helps ER-stressed cells restore protein synthesis (74, 75). Concurrently, cytoplasmic ATF6 released through the ATF6 signaling pathway is essential in controlling genes encoding the components of ERAD (i.e. Derlin-3) (37, 76) .Alternatively, the IRE1/XBP1 pathway triggers protein folding, maturation, and degradation, as well as induces the expression of genes encoding for protein chaperones like Erd (16, 77), p58IPK, EDEM, RAMP-4, PDI-P5, and HEDJ (78). The three sensors and their downstream-dependent pathways and biological sequences are outlined in figure 3.

Apoptosis

Apoptosis is one of three major types of morphologically distinct cell death: apoptosis (type I cell death), the autophagic cell death (type II), and necrosis (type III) (80, 81). All three types are executed through distinct mechanisms with some overlapping signaling pathways in response to specific stimuli (82, 83). Apoptosis is a tightly regulated process that occurs frequently in multicellular organisms and plays an essential role in cell survival (84, 85). The regulation of apoptosis both in normal and tumor cells is mediated by various signaling pathways whose activation is both tissue type and effectors/stimulators-specific (7, 8). The induction of apoptosis in

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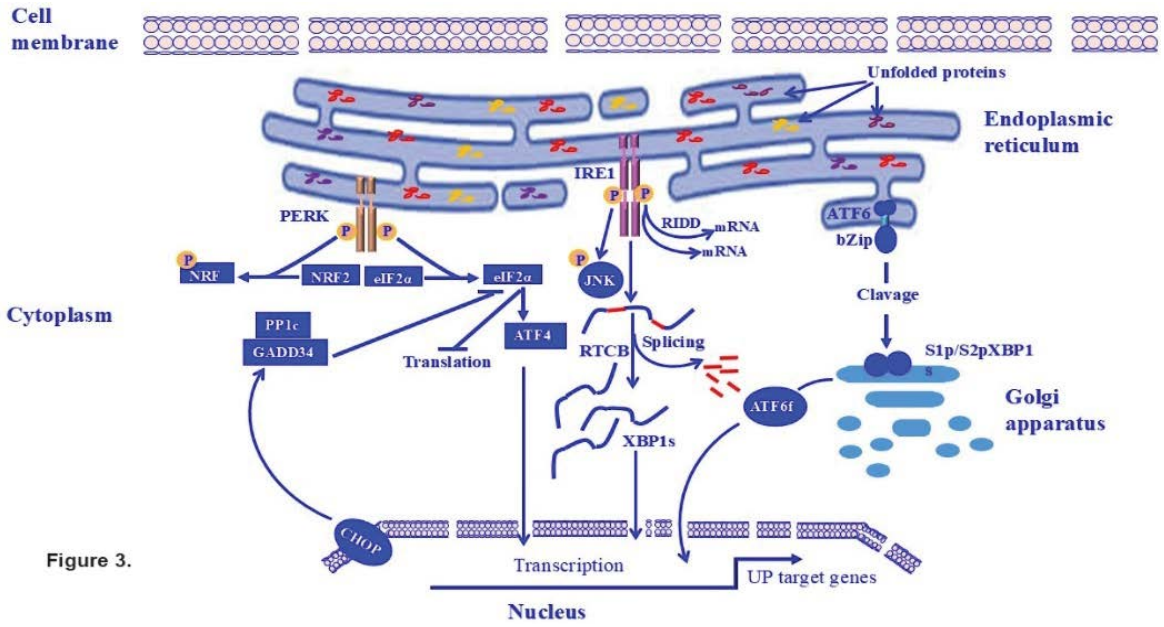

Figure 3.

Figure 3: Endoplasmic reticulum (ER) stress-dependent pathways conditions. The accumulation of misfolded proteins results in the activation of three ER stress sensors: **ATF6** (activating transcription factor-6), **IRE1** (inositol-requiring transmembrane kinase/endoribonuclease 1), and **PERK** (double-stranded RNA-dependent protein kinase)-like eukaryotic initiation factor 2α (eIF2α). The activation of ATF6 is mediated by its cleavage with S1P and S2P, upon which it is transported to the Golgi. Activated ATF6 serves as a transcription factor to induce the expression of ER chaperones and XBP1. Activated IRE1 is essential in triggering the splicing of *XBP1* messenger RNA (mRNA); spliced XBP1 proteins (XBP1s) translocate to the nucleus and control the transcription of ER-resident chaperones and genes involved in the regulation of lipogenesis and ER-associated degradation (ERAD). The main function of activated PERK is to block general protein synthesis *via* phosphorylation of eIF2α and translation of eIF2α-activating transcription factor-4 (ATF4). Thus, once ATF4 is translocated to the nucleus it can induce the transcription of numerous genes required for quality control in the ER.

normal and tumor cells is characterized an enhancement of DNA fragmentation, chromatin condensation, shrinkage of the cytoplasm, and membrane blebbing (86, 87). Apoptotic initiation is mediated by extra- and intracellular signal transduction processes, while its regulation is mediated by an intracellular proteolytic cascade (80, 83). The mechanisms regulating apoptosis are similar across all eukaryotic cells (88, 89). Intracellular regulation is mediated by a family of proteases characterized by their active sites containing cysteine residues; these proteases cleave target proteins/caspases at their specific aspartic acid residues (90, 91). Caspases are target proteins expressed as an inactive protein in the form of pro-caspases (92, 93). The activation of pro-caspases is mediated by their cleavage at aspartic acid residues *via* an upstream caspases-dependent mechanism (90, 94). Activated caspases cleave other key proteins such as nuclear Lamins which leads to an irreversible breakdown of the nuclear lamina (95, 96). While other caspases are known for their ability to cleave proteins, such as the DNA degradation enzymes responsible for inactivating DNase (97, 98). Signaling pathways leading to cell apoptosis or survival are outlined in figure 4.

Mechanisms of apoptosis initiation and execution

In summary, induction of apoptosis is agent-dependent and tissue-specific, whereas its initiation and execution is mediated by either extrinsic or intrinsic pathways-dependent mechanisms (11, 80). While extrinsic and intrinsic pathways are different in their initiation, the mechanisms of their execution are similar (11, 80). Apoptosis induced by the extrinsic pathway is initiated by transmembrane receptor(s) through ligation to corresponding ligand(s) or agonist(s), whereas its progression and execution is mediated by mitochondrial and non-mitochondria-dependent mechanisms (99, 100). In contrast, apoptosis induced by the intrinsic pathway is initiated by a non-receptor dependent signal, and its progression and execution are mediated only by mitochondria- dependent mechanisms (11, 80).

Activation of the extrinsic pathway results from an extracellular signal that occurs following ligand(s)/agonist(s) ligation of membrane receptors (101, 102). The most common membrane receptors and corresponding ligands and agonists include FasL/FasR, TNF-α/TNFR1, Apo3L/DR3, Apo2L/DR4, and Apo2L/DR5 (80, 103). The tumor necrosis factor (TNF) receptor superfamily is one of the best characterized death receptors; all have similar cysteine-rich extracellular domains and cytoplasmic death domains (80, 103). The main function of the extracellular domain is to receive extracellular signals through appropriate ligand or agonist binding, where

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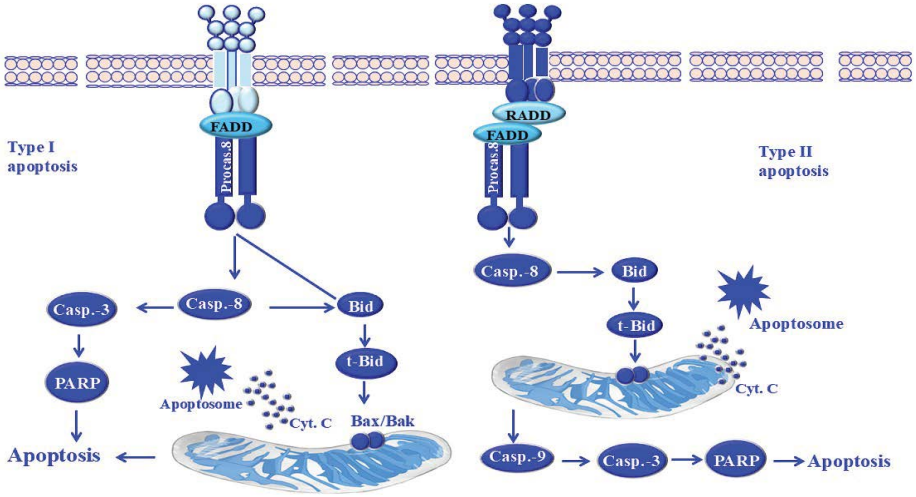

Figure 4: Mechanisms of apoptosis. The regulation of apoptosis via binding of agonists or antagonists (e.g. FASL, TNF-α, or TRAIL) to their corresponding receptors is mediated by two pathways. Once these receptors have been activated, their apoptotic signal can be mediated through the autophosphorylation of procaspase-8 to caspase-8. In type I cells, activated caspase-8 can activate caspase-3, leading to apoptosis. In type II cells, activated caspase-8 can hydrolyze Bid to tBid, tBid interacts with mitochondrial located Bax/Bak, and apoptosis is induced. In the intrinsic apoptosis pathway, DNA damage, growth factor withdrawal, oxidative stress, or toxic damage can destroy the homeostasis of the mitochondria, typically controlled by the Bcl-2 family members, leading to increased mitochondrial membrane permeability allowing cytochrome c release from the intermembrane space of the mitochondria. Released cytochrome c interacts with Apaf-1 and caspase-9 to activate caspase-3 and induce apoptosis.

the death domain transduces the external death signal to the intracellular signaling pathways *via* its cytoplasmic adaptor protein FAS-associated death domain (FADD), recruiting and activating caspase-8 (80, 104). Once caspase-8 is activated, it triggers the activation of both apoptotic pathways. One of these pathways triggers the activation of type I apoptosis, mediated by the activation of caspase-3 and induces PARP cleavage as a marker of apoptotic cell death (80, 105). The other pathway is involved in the initiation of type II apoptosis, mediated *via* a mitochondria-dependent mechanism (80, 106).

Activation of the intrinsic apoptosis pathway is mediated by intracellular signaling which initiate apoptosis *via* two mechanisms (11, 83). One of these mechanisms is mediated by the suppression of inhibitors of cell death machinery, including growth factors, hormones, and cytokines (107, 108). The other mechanism is mediated by the direct action of radiation, toxins, hypoxia, and viral infections in the cell (80, 109). Mitochondrial dysregulation results from the localization of pro-apoptotic proteins such as BH3-only proteins and Noxa protein on the outer mitochondrial membrane which increase mitochondrial membrane permeability and induce the loss of mitochondrial membrane potential (Δψm), cytochrome c (cyt c) release, and the induction and formation of Smac/DIABLO, serine protease HtrA2/Omi, apoptosis inducing factors (AIF), and caspase-activated deoxy-ribonuclease (CAD) (110, 111). The release of these proteins leads to the activation of caspase-9 and caspase-3, with Poly (ADP-ribose) polymerase (PARP) cleavage signaling apoptosis (112, 113). The execution phase of apoptosis is mediated by caspases, cytoplasmic endonucleases, and proteases which degrade nuclear materials and cytoskel et al proteins (11, 80). The mechanisms involved in the regulation of apoptosis by extrinsic and intrinsic apoptotic pathways are outlined in figure 5

Mechanisms of endoplasmic stress-mediated pathways to apoptosis

In addition to their significant role in the modulation of UPR, the ER stress-dependent PERK, ATF6, and IRE1 pathways are essential for the modulation of ER stress-induced apoptosis (34, 114). PERK-dependent signaling pathways have been shown to trigger pro-apoptotic signals that can immediately initiate the mechanisms of cell death machinery, leading to rapid cell death (38, 114). While PERK is essential in phosphorylating eIF2α to enhance protein translation, the main function of IRE1α and ATF6 is to mediate the regulation of ERAD of the PI3K/Akt/mTOR pathways (115, 116). Of note, the continuous activation of PERK, but not those of IRE1α and ATF6, is essential for the regulation of E2-induced apoptosis in response to ER stress (15, 117). Accordingly, sustained activation of PERK triggers the phosphorylation of eIF2α, leading to the activation of ATF4 and the pro-apoptotic protein CHOP (38, 118). The role of PERK in the modulation of ER stress-induced apoptosis is not mediated only through phosphorylation of eIF2α, but also *via* its ability to trigger mitochondrial dysregulation, Ca^{2+}

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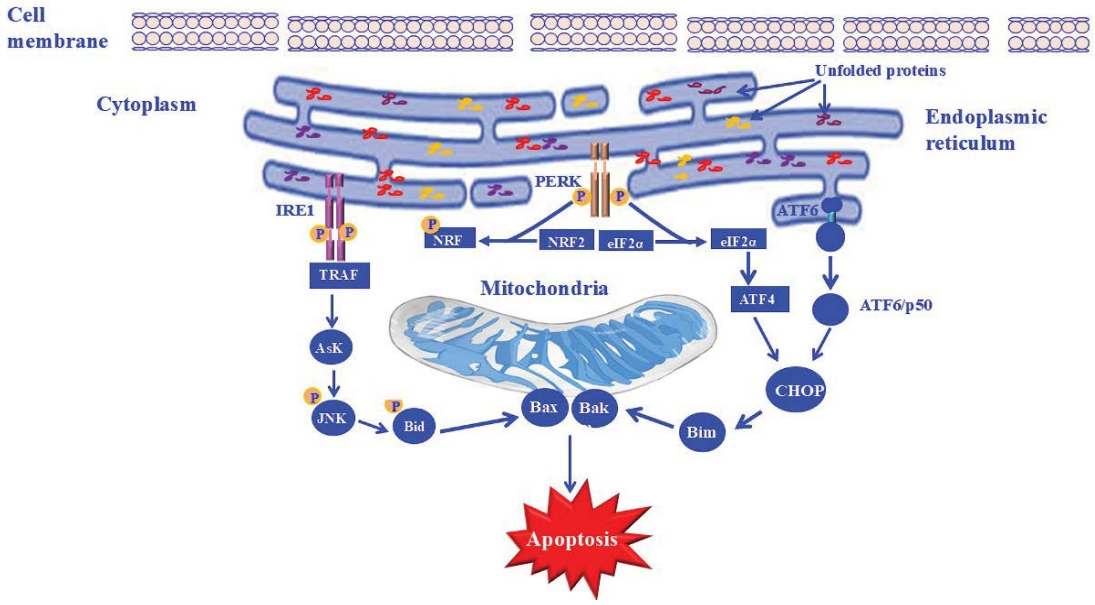

Figure 5: Cell death signaling by the ER stress response/UPR. In case of severe and sustained ER stress, several pro-apoptotic events occur and lead to apoptosis. Transcription factors ATF4 and ATF6-p50 stimulate CHOP expression; CHOP stimulates the expression of GADD34, which associates with PP1, resulting in dephosphorylation of eIF2α and reactivating global cellular protein synthesis. CHOP also inhibits anti-apoptotic proteins of the Bcl-2 family and stimulates pro-apoptotic Bim, altogether leading to heterodimerization and activation of pro-apoptotic Bax and Bak. CHOP stimulates expression of cell surface death receptor DR5, which sensitizes cells to pro-apoptotic stimuli, presumably *via* calibrating the extrinsic apoptotic pathway involving caspase 12. Similarly, activated JNK complements the pro-apoptotic efforts of CHOP. JNK becomes phosphorylated and activated by protein kinase ASK1 upon association of TRAF2 with activated IRE1. Association of TRAF2 with activated IRE1 also leads to activation of caspase 12. Calcium release from the ER *via* Inositol trisphosphate (IP3) receptors can activate calpains, which further stimulate caspase 12 activation *via* proteolytic cleavage of its inactive procaspase precursor.

overload, accumulation of reactive oxygen species (ROS), and the induction of the expression of BH3-only proteins (114, 119).

The ability of continuously activated IRE1 and CHOP to induce apoptosis in cells under physiological and pathophysiological conditions has been described in several studies (34, 155). UPR is primarily a pro-survival response which can switch to apoptosis upon sustained or severe ER stress, either in a UPR-dependent or -independent mechanism (120, 121). ER stress-induced apoptosis is involved in pathological processes of human diseases and is mediated by GADD153, the transcription factor CCAAT, enhancer-binding protein (C/EBP) homologous protein (CHOP), IRE1, and caspase 12 (122, 123). CHOP also stimulates growth arrest and the DNA damage-inducible gene 153 (GADD153) (124, 125). As stated above, apoptosis induced by irreversible ER stress is increasingly recognized as an important pathogenic factor in human diseases like tumors (114, 115). In addition to the adverse environmental conditions caused by tumors, genetic alterations in cancer cells can increase ER stress and promote sustained activation of the UPR signaling pathway (126, 127). Overall, these harsh conditions have been reported to alter the protein folding capacity of the ER in both cancer cells and invading immune cells, promoting UP accumulation and inducing ER stress (127). UPR is activated to restore ER homeostasis and promote adaptation to various tumor insults (129, 130). Many therapies induce ER stress in the cancer cell which alters its normal behavior in the tumor microenvironment (TME) (131, 132). Depending on the extent of ER stress, the cell type, and the specific pathological context, ER stress responses can have different effects ranging from cellular reprogramming and adaptation to autophagy and apoptosis (16, 133). Due to the additive effect of various ER stressors that are simultaneously enriched in the TME during cancer initiation, cancer progression, and cancer therapy, a robust and sustained UPR activation is observed *in vivo* in cancer cells and tumor-infiltrating immune cells, which fail to recapitulate under *in vitro* conditions (134, 135).

Tumor growth and progression is a multi-step process associated with a dramatic increase in protein synthesis and uncontrolled proliferation of tumor cells (136, 137). Consequently, proliferating tumor cells require rapid ER expansion, which enables rapid cell division and allocation of the newly produced tumor cells (28, 138). Controlled regulation of ER stress responses is a dynamic cellular process involving the triggering of opposing cellular functions in tumor cells, leading to either cell survival or death, depending on the strength and duration of the induced UPR (127, 139). We and others demonstrated the mechanisms through which ER stress triggers apoptosis in tumor cells (81, 103, 140, 141).

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The involvement of ER stress-induced apoptosis in head and neck squamous cell carcinoma (HNSCC) is activated in response to treatment with tumor necrosis factor -α (TNF-α). (103) or treatment with imiquimod (81), Bortezomib (140), and Vinblastine (141); ER stress-induced apoptosis is also activated in response to the inhibition of ubiquitin-specific protease 1 in hepatocellular carcinoma (25). ER stress-induced apoptosis in tumor cells is regulated by UPR-induced activation of the IRE1α-TRAF2-JNK pathway (132, 138), or PERK activation which activates IRE1α that, in turn, triggers the activation of ATF-4 to trigger the activation of the transcriptional complex of CHOP (122, 142). This increased expression of CHOP triggers the activation of two parallel pathways, including the CHOP-ERO1α-IP3R1-CaMKII and Bcl-2/Bim axis (115, 143). ER stress can also trigger apoptosis through increased levels of cytoplasmic $Ca2^{+}$, leading to calpain degradation that s initiates the cleavage of caspase-4, caspase-9, caspase-3, and finally apoptosis (114, 144).

Endoplasmic reticulum as therapeutic target for tumor treatment

Numerous ER stress-related proteins and signaling pathways are dysregulated during cancer initiation and development (129, 145). Inhibition of these signaling molecules is thought to slow disease progression, providing exciting potential therapeutic targets. Various classes of cancer therapeutics have been developed which target ER stress pathways (146, 147). Advances in drug discovery have enabled the development of new small molecules that target the enzymatic activity of specific UPR regulators (148, 149). Since aberrant UPR signals are present in cancer, controlling their pharmacological action to limit tumor growth is a very useful strategy. IRE1α, PEEK, and ATF6 are the most promising targets whose inhibition controls disease progression after the UPR onset (129, 150) 129, 151).

BIP/GRP78 is an important molecular chaperone of the UPR, as well as a marker for tumor cells associated with aggressive tumor growth, invasiveness, and metastasis (152, 153). The development of BIP/GRP78-specific inhibitors is therefore considered a possible strategy for cancer treatment. Bip inhibitors, including HA15 and OSU-03012, exhibit increased toxicity to osteosarcoma cells compared to osteoblastic progenitor cells derived from normal bone (154, 155). HA15 induces cancer cell death and inhibits melanoma development both *in vivo* and *in vitro* (155, 156). Another Bip inhibitor, IKM5, has been shown to inhibit breast tumor growth and complement the inhibitory effect of doxorubicin in the early phase of breast cancer therapy (157, 158). The Bip inhibitor KP1339 was approved in Phase I clinical trials as a promising anti-cancer agent (159, 160). Functional analysis of KP1339 in a colorectal cancer model exhibited increased immunogenic cell death (ICD), leading to a sustained immune response against the tumor (161, 162).. Established GRP78 inhibitors, including epigallocatechin gallate (EGCG), have been shown to bind to the ATP-binding structural domain of GRP78 and block its function (163, 164), as well as protect against hormone-related tumors, including breast and prostate cancer (165). Colorectal cancer (CRC) has likewise been inhibited by potassium 3-beta-hydroxy-20-oxopregn-5-en-17-alpha-yl (PHOS, the inhibitor of GRP78 activity) (166, 167). Treatment of the human colorectal carcinoma-derived cell line HCT116 with KP1339/IT-139 was found to induce apoptosis via depletion of GRP78, the key chaperone molecule (167, 168).. In recent years the new inhibitor HA15, known as the main component of thiazolebenzenesulfonamide which inhibits ATPase activity, has been reported to trigger GRP78 (166, 169). HA15 has both antitumor activity and can overcome drug resistance in various tumor types, including breast, pancreatic, adrenal cortex cancer, and melanoma (166, 169). Targeted treatment of GRP78 with HA15 induces apoptosis in lung cancer cells and triggers both ER stress and autophagy (169, 171). There have been several studies on small molecule inhibitors of IRE1, such as STF-083010, which have demonstrated significant antitumor activity in human multiple myeloma (MM) xenografts via inhibition of the endonuclease activity of IRE1 both *in vitro* and *in vivo* (172, 173).

Inhibition of IRE1 RNase activity by the selective inhibitor B-I09 blocks the transmembrane receptor for IRE1 and inhibits leukemia progression in a mouse model of chronic lymphocytic leukemia (CLL) (41, 174). The IRE1α-specific inhibitor 4μ8C, which may block the production of β-catenin, a key factor in the development of colon tumors, suppresses the spread of colon cancer cells (175, 176). In addition, the IRE1α kinase inhibitor compound 18 showed inhibition of tumor growth (114, 127, 173). Another inhibitor of IRE1α RNase activity, stearoyl-CoA desaturase 1 (SCD 1), is effective in attenuating cytotoxicity induced by standard chemotherapeutic agents in Burkitt's lymphoma, characterized by the overexpression of c-Myc (177, 178). Inhibition of IRE1α RNase with MKC8866 inhibitor significantly improves survival in the glioblastoma multiforme (GBM) mouse model (179, 180). Taken together, these preclinical studies suggest that pharmacological inhibitors of IRE1α may be helpful in delaying tumor growth and improving treatment outcomes.

Inhibitors of IRE1 activity target the structural domain of the ATP kinase, an ATP-competitive IRE1α kinase that inhibits RNase attenuators such as sunitinib (180, 181). Although sunitinib has been reported to inhibit VEGF and PDGF, sunitinib can effectively inhibit IRE1 phosphorylation by inhibiting autophosphorylation and subsequently RNase activation (34, 150). In contrast to first-generation IRE1 drugs, second-generation drugs are characterized by their

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ability to directly target the RNase structural domain and inhibit endogenous IRE1α oligomerization, *in vivo* XBP1 mRNA cleavage, and ER-localized mRNA decay in a dose-dependent manner (182, 183). Of note, the inhibitors already identified, including B-I09, STF-083010, 4μ8C, toyocamycin, and a number of MKC compounds, directly target this RNase structural domain and share a common hydroxyarylaldehyde (HAA) fraction (184). B-I09 was approved as anticancer agent due to its potential to control the aggressiveness of chronic lymphocytic leukemia cells *in vivo* (185, 186). The small molecules STF-083010 and 4μ8c exert their inhibitory effects through the formation of a specific lysine residue (Lys907) with the Schiff base in the RNase structural domain. (150, 187). In addition to forming this reversible Schiff base with Lys^{907}, these drugs form hydrophobic contacts with His^{910} and Phe^{889} and hydrogen bonds with Tyr^{892} in the IRE1 RNase structure to inhibit its function. (188, 189). The mechanisms of both small molecules STF-083010 and 4μ8c which lead to IRE1 inhibition are outlined (Fig.6).

ER stress inhibitors have been identified for their therapeutic impact on cancer treatment. As such, STF-083010, MKC-3946, and Toyocamycin inhibit the growth of multiple myeloma (173, 190); likewise, salicylaldehyde MKC-8866 potently inhibits IRE1 RNase activity and exerts tumor suppressive effects, as shown in a mouse xenograft model (PDX) of triple-negative breast cancer (TNBC) (150, 191), as well as a glioblastoma model (179). MKC-8866 induces the regression of breast tumors, particularly those associated with MYC overexpression (179, 192). In addition to these pharmacological inhibitors, kinase-inhibitory RNA enzyme attenuators inhibit IRE1 RNase activity by serving as ATP-competitive ligands, best demonstrated on pancreatic β-cell RNase activity. (34, 193). The main function of peptide fragments of the IRE1cytoplasmic structural domain determines the oligomerization and subsequent RNase activity of IRE1 (34, 194). Functional analysis of methotrexate, cefoperazone, folinic acid, and fludarabine phosphate revealed an inhibition of IRE1 RNase activity *in vitro* and in human glioblastoma cell models due to IRE1 peptide fragment interactions (195, 196). In summary, blocking IRE1 in mouse models is beneficial in inhibiting tumor growth, indicating that targeting UPR may have positive implications for tumor therapy.

Both GSK2606414 and GSK2656157 are common PERK inhibitors and have shown remarkable effects in several studies (133, 197). GSK2656157, often used as a first-line treatment for patients with advanced colon cancer, synergistically inhibits the growth of colon cancer cells with 5-fluorouracil (5-FU) in a mouse model (114, 198). Furthermore, GSK2656157 demonstrated efficacy in overcoming 5-FU resistance of colorectal cancer (CRC) cells to 5-FU treatment (196, 198). A PERK small molecule inhibitor showed excellent antitumor activity in a dose- and time-dependent induction of apoptosis and G2/M cell cycle arrest in a human colon adenocarcinoma cell line, HT-29 (38, 199). As such, PERK inhibitors are expected to have promising anti-tumor effects based on their ability to overcome tumor resistance associated with standard therapies and reduce drug-related side effects (200, 201). GSK2606414, one of the most potent first-generation PERK inhibitors, completely blocks PERK autophosphorylation under extreme ER stress conditions (196, 198). GSK2606414 significantly reduces ATF4, CHOP, and CHOP mRNA expression and blocks the activation of downstream ATF4-CHOP signaling pathways (150, 202). Alternatively, GSK2656157 is a second-generation drug that acts as an ATP-competitive inhibitor of PERK and exhibits antitumor activity in multiple myeloma and pancreatic cancer in immunocompromised mouse xenograft models. This inhibitory effect of GSK2656157 is independent of eIF2α phosphorylation inhibition (204, 205). Additionally, the integrative stress response inhibitor (ISRIB), known as symmetric bis (ethylene glycol) amide, binds and activates elongation initiation factor 2β to trigger the inhibition of protein translation mediated by eIF2α phosphorylation (206, 207). In patient-based models of advanced prostate cancer, ISRIB has been shown to induce tumor regression and prolong patient survival (208, 209). Most promising regarding inhibitors that simultaneously target different kinases is that their molecular effects are well known.

Conclusion

There is increasing evidence that ER stress-induced apoptosis is involved in the pathogenesis or exacerbation of several common disease processes. Studies in this area have provided extensive mechanistic insights into the role of IRE1α and PERK–CHOP -dependent pathways that lead to the induction of apoptosis. Accumulating evidence indicates a role for ER stress-mediated cell death in various diseases like tumors and highlights ER stress dependent pathways as an attractive target for therapies. Many small molecule inhibitors targeting kinase components of the UPR, PERK, and IRE1α are potential drug candidates for cancer treatment. However, targeting only one key molecule of ER stress-dependent signaling pathways may not be sufficient in triggering cell death, necessitating a better understanding of these overall mechanisms.

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