Chapter 3
The Regulation of the Unfolded Protein Response and Its Roles in Tumorigenesis and Cancer Therapy

Jordan Morreall, Feng Hong, and Zihai Li

Abstract The unfolded protein response (UPR) of the endoplasmic reticulum (ER) is a highly conserved system by which cells regulate multiple pathways during misfolded protein accumulation. Acute UPR signaling inhibits translation, induces chaperone expression, and activates proteolysis, whereas chronic UPR signaling can lead to apoptosis. Each of the canonical functions of UPR serves as a mechanism that can limit or facilitate tumorigenesis. Tumor cells are able to coopt UPR signaling to facilitate proliferation, transformation, and epithelial-to-mesenchymal transition (EMT) under hypoxia and glucose starvation, potentially causing metastasis. UPR signaling is typically initiated by Glucose-Regulated Protein 78 (GRP78/BiP) binding to unfolded proteins, causing GRP-78 to dissociate from each of the three primary UPR sensors on the ER membrane: protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring protein 1α (IRE1α). Recent studies highlight the complexity of the signaling interactions involved, but also potential clinical opportunities to target unique molecular interfaces. This review discusses the current understanding of UPR pathways, ongoing clinical approaches to manipulate UPR signaling, and future avenues by which cancer therapy may be advanced by utilizing approaches that target the molecules involved in UPR signaling.

Keywords UPR · ER stress · PERK · ATF6α · IRE1α · BiP · GRP78 · Proteostasis · Redox

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The Roles of the Unfolded Protein Response

The endoplasmic reticulum (ER) is the organelle primarily responsible for protein processing, folding, and transport. In order to carry out protein folding, the ER must maintain an internal environment in which disulfide bonds can form. To do so, ER function relies upon a high calcium concentration, oxidizing conditions, and a variety of chaperone proteins and protein folding enzymes [1, 2]. A variety of extrinsic and intrinsic conditions can inhibit ER function, and thus cause ER stress. ER stress, due to the accumulation of misfolded proteins in the ER, activates a network of pathways termed the unfolded protein response (UPR). Acute UPR activation facilitates the alleviation of the causative ER stress through upregulation of molecular chaperones, downregulation of translation machinery, and induction of the ER-associated degradation (ERAD) system by which misfolded proteins are removed from the ER. However, continued accumulation of unfolded proteins can lead to apoptosis via chronic UPR activation [3].

The first evidence of a coordinated UPR arose from studies illustrating transcriptional upregulation in response to glucose starvation [4]. More evidence came from the discovery that one such glucose-regulated protein was identical to Binding Immunoglobulin Protein (BiP/GRP78/HSPA5), known to bind unfolded proteins [5]. The UPR was first experimentally validated by the demonstration that misfolded hemagglutinin alone could induce the expression of the known ER stress response proteins BiP and 94-kDa Glucose-Regulated Protein (GRP94) [6]. BiP was identified as a protein bound to unsecreted immunoglobulin heavy chains [7], suggestive of its role later identified as a molecular chaperone [8]. Under non-stress conditions, BiP is bound to three ER membrane proteins: PRKR-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring protein 1α (IRE1α). Unfolded proteins in the ER bind free BiP and decrease the steady-state levels of this chaperone, causing it to be released from these sensors, after which they undergo activation and initiation of further signaling cascades [9].

Interestingly, UPR signaling can be initiated by signals independent of ER stress, including Vascular Endothelial Growth Factor (VEGF) stimulation [10]. Likewise, although often the target of PERK, the downstream UPR signaling molecule eukaryotic translation initiation factor 2α (eIF2α) can be phosphorylated by other kinases such as protein kinase R (PKR), activated by binding dsRNA [11]; general control nonderepressible 2 (GCN2) kinase, activated by amino acid depletion [12]; and heme-regulated eIF2α (HRI) kinase, activated by diminished heme levels, typically leading to apoptosis [13]. UPR signaling can also be induced by estrogen signaling through estrogen receptor α (ERα), causing the transient anti-apoptotic opening of ER calcium channels and the upregulation of GRP78/BiP [14]. Nonetheless, UPR signaling is primarily mediated by PERK, Activating Transcription Factor 4 (ATF4), and IRE1α, through which this chapter will describe the functions of the UPR in cancer cells and ways in which its components can be targeted.

Regulation of the Unfolded Protein Response in Cancer Cells

UPR signaling provides several avenues through which cells are able to avoid tumorigenesis. Tumor cells are characterized by a high metabolic rate than can impose ER stress via the rampant production of proteins. However, acute UPR signaling can ameliorate such ER stress, while chronic UPR signaling typically leads to apoptosis, or possibly even H-ras-induced senescence [15]. Nevertheless, some cells undergo oncogenic transformation in a manner that is facilitated by UPR. For example, Myc can stimulate PERK signaling that causes increased protective autophagy and thus cell survival and tumor formation [16].

Tumor cells, particularly those within solid tumors, often proliferate faster than the vascular systems that would provide them with normal cellular oxygenation and glucose supply. Glucose starvation or hypoxia each contributes to a diminished redox potential that limits the formation of disulfide bonds, contributing to an inherent ER stress on hypoxic cells that causes UPR activation [17, 18]. Excess glucose or dietary lipids can also cause an increase in ER stress [19]. The combination of ER stress and glucose starvation induces autophagy, in which cellular components are engulfed and digested, potentially facilitating either cell death or survival [20]. Autophagy is mediated by eIF2α phosphorylation [21].

The high metabolic demands of tumor cell proliferation necessitate increased angiogenesis, which can be mediated through UPR signaling. In addition to hypoxia-stimulated HIF-1, angiogenesis has also been shown to depend on PERK phosphorylation of eIF2α [17]. Moreover, PERK contributes to transcriptional regulation that stimulates angiogenesis within the tumor microenvironment, upregulating transcripts for cellular adhesion protein VCIP, integrins, and factors promoting capillary remodeling [22]. PERK and ATF4 also stimulate the angiogenic factors VEGF, Fibroblast Growth Factor 2 (FGF-2), and Interleukin 6 (IL-6), while inhibiting anti-angiogenic factors such as Thrombospondin 1 (THBS1), Chemokine Ligand 14 (CXCL14), and Chemokine Ligand 10 (CXCL10), as studied under glucose starvation-induced ER stress [23]. Additionally, hypoxia and glucose starvation can stimulate VEGF-A upregulation through IRE1, which substantially affects tumor angiogenesis and proliferation [24]. Blocking IRE1α signaling not only attenuates VEGF-A signaling but also the proangiogenic factors Interleukin 1β (IL-1β), IL-6, and Interleukin 8 (IL-8) [25]. Moreover, IRE1α signaling is involved in the expression of anti-angiogenic molecules such as SPARC, thrombospondin 1, and decorin. All of these molecules are expressed in the matrix and promote mesenchymal differentiation and, paradoxically, the invasiveness of gliomas [25].

IRE1α can play a major role in regulating migration of glioma cells by downregulating stress fibers and RhoA activity, ultimately governing the secretome of cancer cells [26]. Other models of ischemia have illustrated a role for IRE1α inhibiting angiogenesis due to degradation of the transcript for the angiogenic signal netrin-1 via regulated IRE1-dependent decay (RIDD) [27]. PERK and IRE1α, in particular, mediate ER stress signaling that regulates the tumor microenvironment via angiogenesis.

Moreover, breast and lung cancer carcinomas can undergo higher levels of GRP78/BiP expression, poorer differentiation, and a more mesenchymal phenotype. Interestingly, such cells with a more mesenchymal phenotype have a proliferative advantage under complete glucose starvation [28]. Such evidence suggests that the UPR may facilitate the epithelial-mesenchymal transition (EMT) in cancer cells; the EMT is a driver of a metastatic phenotype that is a mechanism of metastasis [29]. Moreover, the ER stress endemic in many tumor cells is not necessarily restricted to the tumor itself. Tumor cells under ER stress may secrete soluble factors that induce ER stress in macrophages, thus potentially stimulating a proinflammatory cellular response within the tumor microenvironment [30]. Furthermore, UPR signaling from tumor cells causes myeloid cells in the tumor microenvironment to become polarized, which limits T cell activation and expansion [31] (Fig. 3.1).

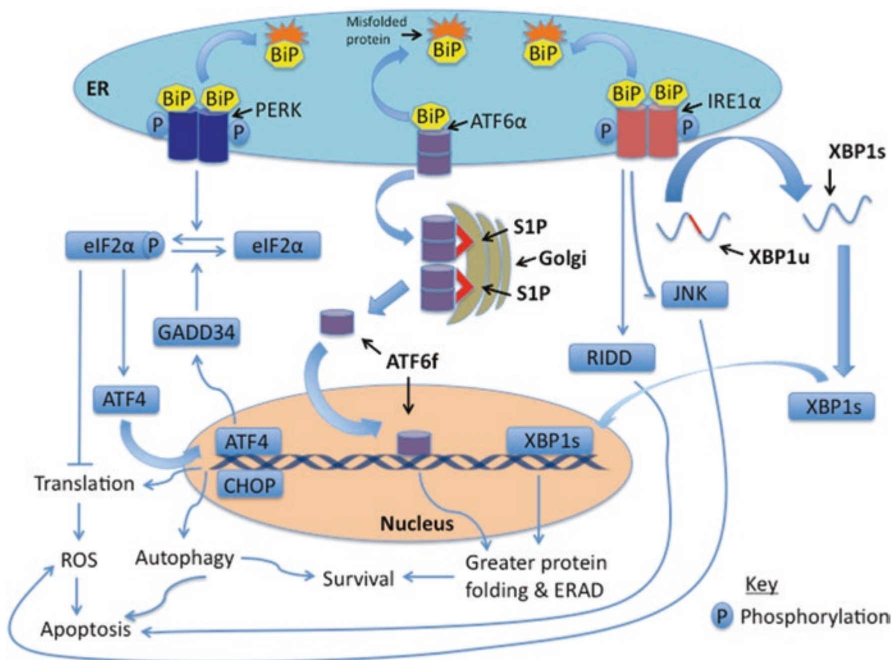

Fig. 3.1 UPR signaling regulates survival and apoptosis. Misfolded proteins are bound by the chaperone GRP78/BiP, which causes its dissociation from PERK, ATF6α, and IRE1α. PERK is then able to undergo dimerization and autophosphorylation, which allows it to phosphorylate eIF2α. Phospho-eIF2α is then able to promote ATF4 signaling via transcriptional regulation with CHOP that facilitates autophagy. Meanwhile, activated ATF6α translocates to the Golgi apparatus, where the S1P and S2P proteases cleave the protein into the active form ATF6f. ATF6f then acts as a transcription factor in the nucleus, where it enhances expression of chaperones and proteins involved in Endoplasmic Reticulum-Associated Degradation (ERAD). IRE1α is also able to undergo dimerization and phosphorylation, allowing it to promote the transcriptional processing of XBP1 transcripts (XBP1u) into the active form XBP1s, which after translation acts as a transcription factor for chaperones and ERAD proteins. ERAD serves as a pro-survival mechanism, while the RIDD and JNK pathways stimulated by IRE1α facilitate apoptotic signaling

PERK Signaling

PERK is a transmembrane protein that contains a serine/threonine kinase domain on its cytosolic face. The cytosolic portion of PERK is bound by heat shock protein 90 (HSP90) in the absence of ER stress, while the portion within the ER lumen is bound by GRP78/BiP. Under ER stress, GRP78/BiP binds unfolded proteins, dissociating from PERK and leaving it free to undergo activation via homodimerization and autophosphorylation [32]. One recent study shows that CNPY2, a ER protein, is dissociated from GRP78/BiP under ER stress, and then binds and activates PERK. [33]. PERK is then able to phosphorylate eIF2α S51, which limits the availability of eukaryotic initiation factor 2 (EIF2)-guanosine triphosphate (GTP)-$tRNA_{met}$ and thus the initiation of translation [11]. This phosphorylation allows tight binding of eIF2α to guanosine diphosphate (GDP), which prevents eIF2B from undergoing GTP binding and exchange and further blocking protein synthesis [34]. The activation of PERK occurs after that of ATF6α and IRE1α [35, 36].

Another consequence of PERK-eIF2α activation is the induction of translation of certain mRNAs, such as ATF4 and proteins that transport amino acids [37]. ATF4 is then able to serve as a transcription factor by upregulating genes important in antioxidant defenses as well as amino acid production [38]. Other targets of ATF4 include growth arrest and DNA damage inducible protein 34 (GADD34), leading to eIF2α dephosphorylation, and CCAAT/enhancer binding protein homologous protein (CHOP) [39, 40]. Induction of CHOP is a major mechanism by which ER stress induces apoptosis [41]. Shortly after the induction of ER stress, PERK also induces microRNA 211 (miR-211), which causes histone methylation that limits CHOP expression, a mechanism by which acute ER stress does not cause the apoptosis seen under chronic ER stress [42].

On the other hand, chronic PERK-eIF2α phosphorylation can lead to apoptosis via CHOP signaling during the diminution of IRE1α and ATF6α signaling, causing decreased tumorgenic potential [11, 35]. CHOP can cause apoptosis by inducing B cell lymphoma 2-interacting mediator of cell death (BIM) while facilitating B cell lymphoma-2 associated X protein (BAX) shuttling to the mitochondria [43, 44]. However, during glucose starvation or hypoxia, diminished PERK levels can lead to decreased tumor cell survival and diminished metabolic ATP production, partly due to limited activation of AKT [45]. Likewise, PERK appears to be an important mediator of EMT by signaling through its downstream effector LAMP3, expression of both of which is critical for metastasis under hypoxia [40]. Interestingly, PERK is also necessary for the regulatory ubiquitination of 40S ribosomal subunits, without which cell survival is diminished during chronic UPR signaling [46].

PERK seems to play an important role in *Neu*-dependent mammary tumor formation and metastasis. However, inactivating PERK increases the frequency of genomic abnormalities, underpinning an increase in spontaneous mammary tumor formation [47]. Activation of PERK increases the frequency of oncogenic transformation induced by MYC via autophagy [16]. Regulation of CHOP by PERK is a critical mechanism of stemming tumorigenesis, as demonstrated in mouse models of lung cancer and hepatocellular carcinoma [48, 49].

ATF6 Signaling

GRP78/BiP binding to unfolded proteins also causes its dissociation from ATF6, allowing the transmembrane protein to shuttle from the ER to the Golgi apparatus. In the Golgi, ATF6 is cleaved into the active transcription factor ATF6f by the proteases site-1 protease (S1P) and site-2 protease (S2P) [50]. Active ATF6f is then able to migrate to the nucleus, where it stimulates the expression of chaperones, X-box binding protein 1 (*Xbp1*), and proteins important in ERAD. An alternative isoform, ATF6β, represses the transcription factor activity of ATF6α [51].

As a transcription factor, ATF6f serves as an important regulator of GRP78/BiP. ER stress causes ATF6f to quickly induce expression of GRP78/BiP, allowing the chaperone to accumulate and dampen UPR signaling while binding unfolded proteins. However, GRP78/BiP is overexpressed in a variety of cancers, and even can be found on the cell surface, causing aberrant signaling [52]. The role of ATF6f regulating GRP78/BiP expression may contribute to its role in promoting hepatocarcinogenesis [53]. Susceptibility to hepatocellular carcinoma is increased in patients carrying a point mutation in *ATF6* that increases ATF6 expression and transcription factor activity [54]. The degree of GRP78/BiP overexpression is correlated with the invasiveness of cancer cells, though also with their responsiveness to therapeutic intervention [55]. Presumably, overexpression of GRP78/BiP allows some cancer cells to maintain high levels of ER stress without the growth-limiting effects of UPR signaling.

IRE1α Signaling

IRE1α is a transmembrane protein that contains a cytosolic serine/threonine kinase domain. Without ER stress, HSP90 (as well as HSP72) binds the cytosolic face of IRE1α, while GRP78/BiP binds to its luminal side [56, 57]. When released from GRP78/BiP, IRE1α undergoes oligomerization and activation of both its endoribonuclease and kinase activities, allowing IRE1α to undergo autophosphorylation [32]. IRE1α is then able to cleave unspliced *Xbp1u* mRNA, removing an intronic sequence that creates a transcript with a frameshift called *Xbp1s* [58, 59]. *Xbp1s* can then be translated into a protein that regulates a number of chaperone and ERAD genes. Interestingly, overexpression of XBP1s inhibits CHOP and thus provides a pro-survival signal [60]. One upstream regulator of XBP1 has been identified in *C. elegans*, a conserved ATPase called RUVB-2, that represses ER stress response via XBP1, and must undergo degradation by the ATPase cell division protein 47 (CDC-48) in order to allow UPR [61].

Although IRE1α signaling facilitates cell survival during acute ER stress, chronic UPR signaling causes diminished IRE1α activation that may lead to apoptosis [62]. One mechanism for the loss of IRE1α activity may be the binding of *Xbp1u* to XBP1s and ATF6α that facilitates their degradation [63]. Nevertheless, apoptosis can arise from chronic IRE1α stimulation as well. IRE1α represses translation by

cleaving transcripts via RIDD, including Ire1α mRNA and Xbp1 mRNA [64, 65]. RIDD also targets microRNAs (miRNAs) such as miR-17, miR34a, miR-96, and miR-125b, and thereby derepresses caspase 2 [66]. Another avenue through which IRE1α could induce apoptosis is through binding tumor necrosis factor receptor-associated factor 2 (TRAF2), recruiting apoptosis signal-regulating kinase 1 (ASK1) and JUN N-terminal kinase (JNK), which activates BIM while inactivating B cell lymphoma 2 (BCL-2) [67].

IRE1α plays a critical role through XBP1 signaling in stimulating the differentiation of mature B cells into plasma cells, as well as the maintenance of B cell immunity [68, 69]. High XBP1s expression is associated with the development of multiple myeloma [70]. In human multiple myeloma cell lines, loss-of-function mutations in IRE1α or XBP1s increase resistance to proteasome inhibitors, a standard treatment [71]. *IRE1A* loss-of-function mutations have also been found in a variety of other cancers, while XBP1 is known to suppress gut tumorigenesis in mice [72, 73]. Conversely, high expression of XBP1 is implicated in triple-negative breast cancer, suggesting that XBP1 may play a role in promoting stem-like phenotypes [74]. Furthermore, diminished levels of XBP1 have been observed to prevent the differentiation of myeloma cells, characteristic of tumor cells, whereas the activation of the intact UPR stimulates myeloma cell differentiation [75].

Coordination of Signaling from PERK, ATF6, and IRE1α

The central coordination of UPR signaling lies in the upstream regulator GRP78/BiP. Cancer cells are able to diminish apoptotic signaling that arises from UPR activation through overexpression of GRP78/BiP [76]. However, recent studies have identified other shared UPR regulators. cAMP response element binding protein (CREB) regulates PERK and IRE1α by binding their promoters and controlling their expression. CREB has been identified as an important contributor to both UPR-mediated lung metastasis and ER stress-induced cell death [77]. Similarly, transmembrane protein 33 (TMEM33) is upregulated in response to ER stress, binds to PERK, increases pro-apoptotic caspase signaling, and activates IRE1α and eIF2α [78].

Chronic UPR in normal cells causes dwindling signals from IRE1α and ATF4, allowing CHOP induction from PERK signaling to cause apoptosis [35]. Some cancer cells evade apoptosis through constitutively active IRE1α signaling [79]. The upregulation of CHOP induces the AKT antagonist TRIB3 and thereby blocks proliferative mTOR signaling to cause autophagy [80]. The translation inhibition caused by eIF2α phosphorylation limits cyclin D1 availability, causing G1 arrest [81]. In this way, UPR activation in cancer cells may promote a quiescent phenotype allowing survival under stress conditions. On the other hand, some cancer patients have been identified in whom RIDD deficiency permitted tumor cell survival by escaping apoptosis [82].

The activation of some branches of the UPR can also stimulate its other branches. For example, the activation of PERK and eIF2α leads to increased levels and trafficking of ATF6α [83]. Androgen signaling can also simultaneously affect several branches of UPR signaling. One study identified androgen receptor signaling as activating IRE1α in a pro-growth manner while inhibiting PERK in prostate cancer cells, as well as a correlation between androgen receptor and UPR gene expression [84]. The modulation of multiple UPR branches can also occur from signaling by cell cycle regulators such as cyclin D1, which promotes ER stress-induced apoptosis [85]. ER stress-induced apoptosis involves decreasing levels of apoptosis-inducing E2F1, mediated by ATF6 and IRE1, during the later stages of ER stress response. The knockdown of E2F1 causes increased ER stress-induced apoptosis [86].

Pharmacological Interventions in UPR Biology

The UPR involves complex signaling that has been implicated in a variety of pathologies. However, since the activation of the UPR can have both pro-survival and pro-apoptotic effects, there is considerable complexity in the pharmacological intervention in cancer UPR signaling. ER stress is found at higher levels within many tumor cells, especially in cells with a secretory phenotype such as multiple myeloma. Such cells rely on a continuous induction of cellular proliferation and signaling that causes ER stress. Many tumor cells can therefore be targeted by imposing ER stress, which can cause cells already under ER stress to undergo apoptosis. For example, bortezomib is a 26S proteasome inhibitor that is used widely to treat multiple myeloma and mantle cell lymphoma. Bortezomib induces the expression of CHOP, PERK, and ATF4 in multiple myeloma cells [87]. IRE1α and XBP1 are both necessary in order for cells to be sensitive to such proteasome inhibitors since tumor preplasmablasts rely on these proteins in order to undergo maturation into immunoglobulin-secreting B cells [71]. On the other hand, the reliance of tumor cells on ER function can leave them vulnerable to inhibition of ER components (Table 3.1).

PERK Signaling

PERK signaling can be stimulated by a range of insults, exemplified by clinical techniques to upregulate PERK that now can involve non-pharmacological means. For instance, while conventional radiation has considerable systemic dose-limiting toxicity, heavy ion radiation is able to induce localized cytotoxic autophagy with great efficiency, an effect which is partly mediated by stimulating the UPR via the PERK axis while inhibiting Akt-mTOR [127]. This technique is limited by the availability of heavy ion radiation, although it has shown greater efficacy than traditional radiotherapy. Another therapeutic agent that can induce apoptosis by

Table 3.1 Pharmacological interventions in UPR signaling

Target	Drugs	Secondary targets and references	Cancer clinical trials
UPR induction	Sorafenib	Induces cytotoxic VCP phosphorylation [88]	FDA approved for renal carcinoma and hepatocellular carcinoma
GRP78/BiP expression	Versipelostatin	Inhibits induction of GRP78/BiP and UPR signaling in glucose-starved cells [89]	Preclinical
	PAT-SM6	Binds to BiP on cancer cell surface [90]	Phase 1/2 in multiple myeloma
	DHA	• Blocks surface GRP78 expression • Inhibits PERK [91]	Phase 2/3 in solid tumors
	Arctigenin	• Blocks the induction of BiP and GRP94 during glucose starvation • Prevents AKT activation during glucose starvation [92]	Preclinical
	EGCG (epigallocatechin gallate)	Targets GRP78/BiP ATP-binding domain [93]	Phase 1/2
	Nelfinavir	• Inhibits HSP90 • Inhibits S2P and thereby induces ATF6 • Activates caspases 3, 7, and 8 • Inhibits AKT, causing diminished VEGFA and HIF1α [94]	Phase 1/2 in solid tumors and multiple myeloma
Proteasome	Carfilzomib	• Promotes NF-κB activation • Induces pro-apoptotic BCL2-Interacting Killer (BIK) and anti-apoptotic Myeloid Cell Leukemia 1 (MCL1) [95]	FDA approved for multiple myeloma; Phase 1/2 in hematopoietic malignancies and lung cancer
	MLN9708	• Activates caspases 3, 8, and 9 • Upregulates p53, p21, NOXA, p53-Upregulated Modulator of Apoptosis (PUMA), and E2F • Inhibits NF-κB [96]	Phase 1 in solid tumors; Phase 1/2 in hematopoietic malignancies; Phase 3 in multiple myeloma
	Marizomib	Upregulates caspase 8 and ROS-mediated apoptosis [97]	Phase 1 in solid tumors and hematopoietic malignancies; Phase 1/2 in multiple myeloma
	Falcarindiol	Inhibits proteasome [98]	Preclinical

(continued)

Table 3.1 (continued)

Target	Drugs	Secondary targets and references	Cancer clinical trials
	NPI-0052	Blocks NF-κB activity [99]	Phase 1 in solid tumors and hematopoietic malignancies; Phase 1/2 in multiple myeloma
	Bortezomib	• Inhibits IRE1α–XBP1 and NF-κB pathways • Induces expression of NOXA • Triggers immunogenic cell death [100]	FDA approved for multiple myeloma and mantle cell lymphoma; Phase 1/2 in solid tumors
	MG-132	Cytotoxic activation of UPR [101]	Preclinical
PERK and eIF2α phosphorylation	GSK2606414	Inhibits active site of PERK [102]	Preclinical
	6-shogaol	• Promotes light chain 3 (LC3) cleavage • Induces cell death through autophagy [103]	Preclinical
	GSK2656157	• Binds PERK ATP-binding site [104]	Preclinical
HSP90	AT13387	• Promotes senescence • Represses epidermal growth factor receptor (EGFR), AKT, and Cyclin-Dependent Kinase 4 (CDK4) • Induces p27 [105]	Phase 1/2 in solid tumors
	17-AAG	Apoptotic UPR activation [106]	Phase 2/3
	Tanespimycin	• Blocks 20S proteasome chymotrypsis • Limits cell proliferation via BRAF expression • Interferes with VEGFA and causes apoptosis [107]	Phase 1/2 in solid tumors and hematopoietic malignancies; Phase 3 in multiple myeloma
	SNX-5422	NA [108]	Phase 1 in solid tumors and hematopoietic malignancies; Phase 2 in TP53-null tumors
	Ganetespib	• Inhibits AKT • Represses HIF1α and signal transducer and activator of transcription 3 (STAT3) [109]	Phase 1/2 in solid tumors and hematopoietic malignancies; Phase 3 in non-small-cell lung cancer, Acute Myeloid Leukemia, andMyelodysplastic Syndrome

(continued)

Table 3.1 (continued)

Target	Drugs	Secondary targets and references	Cancer clinical trials
	AUY922	• Suppresses AKT and ERK only in Phosphatase and Tensin homolog (*PTEN*)-null esophageal squamous cancer cells • Inhibits NF-κB • Promotes apoptosis by repressing Rapidly Accelerated Fibrosarcoma 1 (RAF1) [110]	Phase 1/2 in solid tumors and hematopoietic malignancies
	PU-H71	• Represses AKT, ERK, RAF1, MYC, KIT, Insulin-Like Growth Factor 1 Receptor (IGF1R), Telomerase Reverse Transcriptase (TERT) and Ewing sarcoma-Friend Leukemia Integration 1 (EWS–FLI1) in Ewing sarcoma cells • Facilitates degradation of Inhibitor of nuclear factor Kappa-β Kinase subunit β (IKKβ) and activated AKT and B Cell Lymphoma Extra large (BCL-X) [111]	Phase 1 in solid tumors and hematopoietic malignancies
	Debio 0932	NA [112]	Phase 1 in solid tumors and hematopoietic malignancies
	XL888	• Facilitates degradation of CDK4 and WEE1 • Inhibits AKT signaling • Increases BIM expression and decreases MCL1 expression [113]	Phase 1 in melanoma
	IPI-504	• Binds to ATP-binding site on HSP90 • Disrupts transcription factor activity of XBP1 and ATF6 • Interferes with PERK phosphorylation of eIF2α • Limits BiP buildup [114]	Phase 1/2 in solid tumors and hematopoietic malignancies; Phase 3 in gastrointestinal stromal tumors
Pan-deacetylase	Panobinostat	• Induces BiP, ATF4, and CHOP, IRE1α and eIF2α activation • Induces BIK, BIM, BAX, Bcl-2 Antagonist/Killer (BAK), and caspase 7 activity [115]	FDA approved for multiple myeloma; Phase 1/2 in solid tumors and hematopoietic malignancies; Phase 3 in hematopoietic malignancies

(continued)

Table 3.1 (continued)

Target	Drugs	Secondary targets and references	Cancer clinical trials
WNT signaling	Pyrvinium	• Represses BIP and GRP94 induction during glucose starvation [116]	FDA-approved anthelmintic agent; preclinical for cancer
Anti-diabetic biguanides	Metformin	• Represses XBP1 and ATF4 under glucose starvation [117]	FDA-approved anti-diabetes drug; Phase 1/2 in solid tumors and hematopoietic malignancies; Phase 3 in solid tumors
IRE1α	Sunitinib	Pro-proliferative kinases [118]	Phase II for multiple myeloma; FDA approved for renal cell carcinoma
	STF-083010	• Limits endonuclease activity of IRE1 endonuclease [119]	Preclinical
	MKC-3946	• Impedes IRE1α endonuclease domain • Increases apoptosis when coadministered with bortezomib and 17-AAG [120]	Preclinical
	Toyocamycin	• Cytotoxic inhibition of *XBP1* mRNA splicing [121]	Preclinical
	4μ8C	Inhibition of *XBP1* mRNA splicing [122]	Preclinical for multiple myeloma
	MKC-3946	• Inhibition of *XBP1* mRNA splicing • Sensitization to bortezomib [123]	Preclinical for multiple myeloma
VCP	DBeQ	• Buildup of ubiquitinated proteins and LC3-II [124]	Preclinical
	ML240	• Buildup of ubiquitinated proteins and LC3-II [125]	Preclinical
	Eeyarestatin	• Induction of UPR genes • Buildup of ubiquitinated proteins • Increased bortezomib sensitivity • Inhibits tumor growth [126]	Preclinical

Major avenues of pharmacological interventions in cancer include proteasome inhibition, inhibition of the UPR regulators HSP90 and GRP78/BiP, and inhibitors of the downstream signaling molecules PERK and IRE1

stimulating PERK signaling is farnesol, which caused cytotoxicity in a leukemia model [128]. Although farnesol is appealing in its natural availability, it has so far been shown to have limited efficacy.

Several PERK modulators have been developed with promising results. For example, GSK2656157 has high specificity for PERK inhibition and targets tumor vasculature, though human use would be limited by pancreatic dysfunction [129]. Future therapeutics may be able to target upstream activators of PERK such as the ER-resident thiol oxidoreductase ERp57, which catalyzes the formation of disulfide bonds, the knockdown of which causes cell death via PERK activation [130]. Likewise, the triterpenoid compound celastrol induces apoptosis in a PERK-dependent manner [131]. Another class of compounds, sulfonamidebenzamides, has been identified as selectively upregulating the CHOP pathway downstream of PERK and inhibiting proliferation in a number of cancer cell lines [132]. Induction of the UPR also has considerable therapeutic value, demonstrated by the efficacy of borrelidin, a threonyl-tRNA synthetase (ThRS) inhibitor that increases XBP1 splicing and causes increased eIF2α activation in an oral squamous cell carcinoma model, in which PERK expression conferred sensitivity to borrelidin [133].

UPR induction can also be mediated by the induction of both metabolic and ER stress, such as by administration of the inhibitory glucose analog 2-deoxy-D-glucose (2DG) that also inhibits N-glycosylation. 2DG has been utilized in studies of Acute Lymphocytic Leukemia (ALL), in which treatment leads to apoptosis via UPR signaling, particularly among BCR-ABL+ ALL cells [134]. Given the limited types of cells sensitive to 2DG, it remains to be seen whether such targeted therapy may hold clinical promise.

ATF6 Signaling

ATF6 signaling is currently an underdeveloped avenue of pharmacological intervention in cancer. Nevertheless, nelfinavir inhibits its downstream target S2P and causes accumulation of ATF6 by preventing its conversion to the active cleavage product ATF6f [135]. Because of the high growth rate of tumor cells, the deprivation of a single amino acid can dramatically reduce their growth potential while posing minimal risk of toxicity for the patient. One such methodology is arginine starvation, which induces chronic ER stress via IRE1α and ATF6 in cancer cell lines. However, arginine starvation alone appears to be relatively cytostatic, so in order to induce toxicity, studies have supplemented this therapy with the arginine analog canavinine, which may enhance its efficacy [136].

IRE1α Signaling

Estrogen receptor signaling is especially important in breast cancer, in which resistance to chemotherapeutics and UPR activation are associated in triple-negative breast cancers. Estrogen receptor β 1 (ERβ1) induces the degradation of IRE1α, underlying the association between IRE1α levels and activity and the survival of ERβ1 positive cells. While ERβ1 promotes ER stress-induced apoptosis, estrogen receptor α (ERα) regulates XBP1 expression. These findings illustrate an opportunity to regulate UPR-associated breast cancer survival by targeting ERβ1 [137]. Another intriguing connection between IRE1α and estrogen signaling lies in the poor clinical response of breast cancer samples with high XBP1 levels to the estrogen receptor antagonist prodrug tamoxifen. A compound was developed called STF-083010 to inhibit XBP1 splicing and has been found to restore tamoxifen sensitivity in resistant MCF-7 cells. Coadministration of STF-083010 with tamoxifen gave considerable efficacy in a mouse xenograft model [138].

Conversely, activation of IRE1α may also provide a therapeutic benefit. A compound called LU-102 was developed in order to overcome therapeutic resistance to the proteasome inhibitor bortezomib, caused by a compensatory upregulation of the untargeted proteasomal subunits. Combinatory administration of LU-102 with standard proteasome inhibitors yielded synergistic cytotoxicity via apoptosis induced by IRE1α activity [139]. Bortezomib gives rise to resistant cellular subpopulations in clinical cases although interestingly the coadministration of the demethylating agent 5-azacytidine is able to eliminate much of this resistance [140].

Another mechanism of therapeutically inducing ER stress is the inhibition of histone deacetylase (HDAC) activity, causing the aggregation of misfolded proteins. Particularly in combination with bortezomib, HDAC6 inhibitor ACY-1215 provided a significant delay in tumor growth and prolonged survival in mouse models of lymphoma. Interestingly, the same study illustrated increased XBP1 expression in tumor samples [141]. Redox manipulation provides another avenue of imposing ER stress. The small molecule SK053 was developed in order to target the thioredoxin-thioredoxin reductase system and has considerable efficacy against tumors in mice. By imposing oxidative and ER stress, treatment of tumor cells increases BiP, CHOP, and XBP1s levels, causing apoptosis correlated with the cellular levels of thioredoxin [142]. Another small molecule that appears to target XBP1s is 17#, a small molecule that inhibits tumor growth in vitro and in xenografts synergistically with doxorubicin, etoposide, and 2-deoxy-D-glucose [143].

Coordinated Signaling from PERK, ATF6, and IRE1α

Inhibition of targeted individual branches of the UPR may provide greater clinical efficacy against tumors known to rely on such signaling, In the absence of such information, targeting multiple UPR branches may offer a more useful clinical approach.

Although no pharmacological TMEM33 inhibitors have yet been described, a variety of CREB inhibitors hold promise as a means to target global UPR signaling and sensitivity to apoptosis arising from ER stress [144, 145]. In an ovarian cancer cell line model, β-phenethyl isothiocyanate (PEITC) causes an increase in reactive oxygen species (ROS) and inhibits proliferation by increasing apoptosis via upregulating either PERK or ATF-6 in one model or PERK and IRE1α in another [146]. Likewise, PERK and IRE1α are inhibited by the hepatocellular carcinoma (HCC) therapeutic Sorafenib in HCC cell lines [147]. Conversely, some therapeutic compounds are able to activate each branch of the UPR simultaneously. For example, 3,3-bis(4-hydroxyphenyl)-7-methyl-1,3-dihydro-2H-indol-2-one (BHPI) is a compound that inhibits ERα-controlled gene expression while inducing chronic ER stress via ERα activation and opening of ER calcium channels. The induction of all three branches of UPR signaling induces apoptosis that causes rapid tumor regression among drug-resistant ERα-expressing breast cancer cells in a mouse xenograft model [148].

One way to target global UPR signaling is to target upstream regulators of its activation. In particular, GRP78/BiP may serve as a promising target, particularly for its role in regulating tumor cell autophagy and apoptosis. Inhibition of GRP78/BiP causes increased apoptosis in a mouse model of colon cancer [149]. Pharmacological methods of blocking BiP induction, such as with arctigenin, are especially promising for tumors that depend on UPR to manage proteotoxic stress [92]. Another piece of evidence that GRP78/BiP inhibition has therapeutic value has arisen from studies of drug combination therapy. The coadministration of bortezomib and the antidiabetic agent metformin suppresses the induction of GRP78/BiP, enhances apoptosis, and increases susceptibility to bortezomib in a sample of clinical myeloma tumor cells and xenografts [150].

Several other therapeutics target GRP78/BiP, including docosahexaenoic acid (DHA), which blocks surface GRP78 expression as well as inhibiting PERK [91]. Limited clinical trials have been completed, but targeted combinatory therapy is ongoing in several clinical trials. The antibody PAT-SM6 is another therapeutic that targets cell surface GRP78/BiP expression [90]. Although the primary endpoint of the current PAT-SM6 clinical study is stable disease, that endpoint was reached with the goal of establishing optimal dosage for future clinical trials. The induction of GRP78/BiP is another therapeutic target, inhibited by the preclinical compound versipelostatin [89]. Other therapeutics have been designed to target the ATP-binding domain of GRP78/BiP, including epigallocatechin gallate (EGCG) [93]. Although EGCG has been ineffective in clinical trials targeting smoldering multiple myeloma, it has been effective in therapy to clear HPV and low-grade cervical neoplasia. Future clinical trials could capitalize on the simultaneous inhibition of GRP78/BiP and GRP94 by the administration of pyrvinium [116]. As a counterpart to targeting BiP/GRP78, inhibitors have also been developed that target the other major regulator of PERK and IRE1α, HSP90. One such inhibitor, 17-*N*-allylamino-17-demethoxygeldanamycin (17-AAG, or Tanespimycin), has shown limited clinical response in trials to date, but hope remains for the identification of patient subgroups who may be best able to benefit from its effects, especially in combination therapy [106]. One interesting cache of 17-AAG is its selectivity for HSP90 in

tumor cells, in which the protein is uniquely found in multichaperone complexes that have selectively high affinity for 17-AAG [151].

The Future of Cancer Intervention via UPR-Modulatory Drugs

Pharmacological interventions in tumor cell ER function are advancing rapidly. Advances in tumor cell targeting are being advanced particularly by the development of immunogenic therapies. Current therapeutics illustrate the tumor specificity of such therapies, including ER stress-associated anthracyclin induction of cell surface calreticulin expression, important for tumor cell phagocytosis by dendritic cells and immunogenicity in a mouse model [152]. UPR-targeting compounds have some intrinsic specificity for tumor cells given the high levels of ER stress found in tumor cells, thus making UPR inhibition pro-apoptotic in both tumor cells in general and specifically in secretory cells such as those in multiple myeloma [153]. One salient example of tumor cell specificity is the cell-surface expression of BiP found only in tumor cells, giving BiP inhibitors high tumor specificity [52].

However, the limitations of such approaches principally arise from the outgrowth of resistant tumor subpopulations. Resistance to drugs can be caused by factors including modification of target proteins, increased degradation or export of drug molecules, or amplification of cellular machinery that compensates for the targeted molecular signaling. The modification of target proteins can either occur at the transcriptional level via mutations or at the post-translational level. Resistance can be combated by combination therapy, such as the inhibition of PERK in radioresistant hypoxic tumor cells [154]. Combination therapy can be tailored to overcome resistance to a range of therapies, such as oncolytic virus resistance in glioblastoma cells that can be overcome by the inhibition of IRE1α [155].

There are many UPR-related phenomena for which ongoing therapeutic development may be effective. For example, UPR signaling can stimulate inflammation via NF-κB, whose inhibition in metastatic cancer can cause inflammatory tumor growth to give way to inflammation-promoted regression [156]. Although exclusive targeting of NF-κB may be therapeutically limited, drugs such as bortezomib have shown efficacy partly through such inhibition of inflammatory factors such as NF-κB [157]. Moreover, drugs in clinical trials such as AUY922 are able to induce anti-tumorigenic apoptosis via RAF-1 inhibition while inhibiting inflammation via NF-κB [110].

While therapy is able to manage cancer cases, cancer prevention can limit its development by guiding individuals toward anti-tumorigenic lifestyle choices. For example, cigarette smoke induces considerable UPR dysregulation both in vivo and in clinical cases, and decreasing exposure would mitigate the tumorigenic consequences [158]. Likewise, the modification of diet can allow individuals to manage their cancer risk by including compounds such as epigallocatechin gallate, a polyphenol found in green tea that has considerable anticancer properties [159] and targets the ATP-binding domain of BiP [93]. Implementing cancer prevention strategies that leverage our developing understanding of UPR in cancer will allow us to

limit cancer incidence. Meanwhile, thorough characterization of the mechanisms by which cancer cells are able to exploit UPR signaling will provide opportunities to better target the diversity of clinical cases that arise.

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