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REVIEW

# Endoplasmic Reticulum Stress–Activated Cell Reprogramming in Oncogenesis

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**ABSTRACT** Stress induced by the accumulation of unfolded proteins in the endoplasmic reticulum (ER) is observed in many human diseases, including cancers. Cellular adaptation to ER stress is mediated by the unfolded protein response (UPR), which aims at restoring ER homeostasis. The UPR has emerged as a major pathway in remodeling cancer gene expression, thereby either preventing cell transformation or providing an advantage to transformed cells. UPR sensors are highly regulated by the formation of dynamic protein scaffolds, leading to integrated reprogramming of the cells. Herein, we describe the regulatory mechanisms underlying UPR signaling upon cell intrinsic or extrinsic challenges, and how they engage cell transformation programs and/or provide advantages to cancer cells, leading to enhanced aggressiveness or chemoresistance. We discuss the emerging cross-talk between the UPR and related metabolic processes to ensure maintenance of protein homeostasis and its impact on cell transformation and tumor growth.

**Significance:** ER stress signaling is dysregulated in many forms of cancer and contributes to tumor growth as a survival factor, in addition to modulating other disease-associated processes, including cell migration, cell transformation, and angiogenesis. Evidence for targeting the ER stress signaling pathway as an anticancer strategy is compelling, and novel agents that selectively inhibit the UPR have demonstrated preliminary evidence of preclinical efficacy with an acceptable safety profile. *Cancer Discov; 5(6); 1–12. ©2015 AACR.*

## CANONICAL ER STRESS SIGNALING, ACTIVATION MECHANISMS, AND ALTERATIONS IN CANCERS

Since the discovery of an adaptive response against disrupted endoplasmic reticulum (ER) homeostasis through the upregulation of specific ER-resident chaperones (1), the so-called "ER stress response" has been the subject of many studies and reviewed extensively. ER stress results from the imbalance in the folding capacity of this organelle, thus leading to the accumulation of improperly folded proteins in its lumen. To restore ER proteostasis, the cell has evolved an integrated signaling network named the unfolded protein response (UPR; ref. 2). The UPR is mainly transduced by three ER-resident sensor proteins, protein kinase R–like endoplasmic reticulum kinase (PERK; ref. 3), activating transcription factor 6 alpha (ATF6α; ref. 4), and inositol requiring enzyme 1 alpha (IRE1α, called IRE1 hereafter; ref. 5; Fig. 1). The integrated signaling downstream of these three sensors tightly controls life-or-death decisions in cells exposed to either oncogenic (oncogene or tumor suppressors) or environmental (hypoxia, nutrient deprivation, pH) stresses. The mechanisms involved in sensing stress by the three UPR sensors are controlled by the ER chaperone BiP/GRP78. Under basal conditions, BiP constitutively binds to the three sensors, thus preventing their activation. Under ER stress, BiP dissociates from IRE1, PERK, and ATF6, thereby allowing their respective oligomerization and autotransphosphorylation (6) or revealing an ER export motif in ATF6 (7).

### PERK Signaling

PERK oligomerization induces its autophosphorylation and the subsequent phosphorylation of the translation initiation factor EIF2α, thereby attenuating global protein synthesis (8). Phosphorylation of EIF2α and reduction of global

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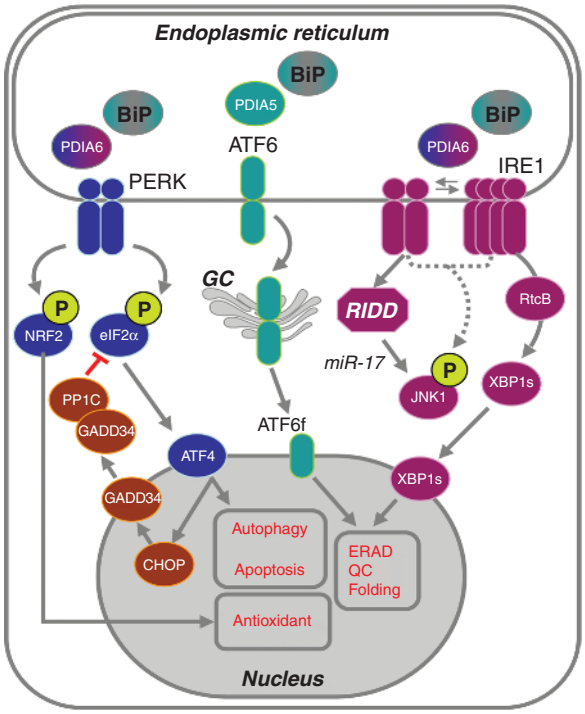


**Figure 1.** Schematic representation of the UPR. Purple, IRE1-dependent pathways; blue, PERK-dependent pathways; green, ATF6-dependent signals. Orange signs represent the negative feedback loop activated downstream of PERK to dephosphorylate eIF2α and restore translation. UPR target functions are indicated in red. Dual-color signs indicate the contribution to more than one pathway following the same color code as described above. GC, Golgi complex; QC, quality control.

translation also allows the bypass of a μORF upstream of the ATF4 start codon, leading to the selective translation of ATF4 (9). ATF4 is a transcription factor that controls the expression of genes involved in folding, antioxidant responses, autophagy, amino acid metabolism, and apoptosis (10). In addition, ATF4 promotes the transcription of *CHOP* and *GADD34*; the former is thought to control a proapoptotic response (11), whereas the latter is instrumental in the dephosphorylation of eIF2α together with the phosphatase PP1c (12). Moreover, active PERK directly phosphorylates NRF2, which subsequently controls the antioxidant response pathway (13–15). More recently, PERK activation has been shown to lead to the phosphorylation of the transcription factor FOXO (16), thereby leading to enhanced FOXO activity and to decreased insulin responsiveness in *Drosophila melanogaster*. In a similar manner, a cryptic lipid kinase activity was recently uncovered in PERK, thereby promoting the phosphorylation of diacylglycerol (DAG) and its conversion to phosphatidic acid (17). Although these two observations were made in a metabolic context, either insulin resistance in *D. melanogaster* or adipocyte differentiation, their impact on cancer cell metabolism might represent novel paths for therapeutic development. In summary, PERK signaling in cancer has been shown to contribute to adaptive pathways rather than to cancer cell death, as demonstrated by the fact that pharmacologic inhibition of PERK attenuates tumor growth in mouse xenograft models (18, 19).

## ATF6 Signaling

ATF6 is a membrane-anchored transcription factor whose activation mainly controls ER protein folding and quality-control machineries. ATF6 activation upon ER stress requires export from the ER and cleavage in the Golgi apparatus by the proteases S1P and S2P (20, 21). Moreover, ATF6 export from the ER also depends on its cysteine oxidation status (22) as well as on protein disulfide isomerase A5 (PDIA5; ref. 23). The ATF6 cytosolic domain (ATF6f) translocates to the nucleus, where it activates specific transcriptional programs involved, for example, in ER-associated degradation (ERAD; refs. 24, 25). ATF6 belongs to a family of transmembrane transcription factors that comprises about 10 members with different functions in stress response (26). Recently, BBF2H7/CREB3L2, which is activated in a similar manner to ATF6, was found to exert its function not only through its transcription factor domain (27) but also through its luminal domain, which is secreted and acts as a growth factor (28). The main functions of ATF6 to date depend on its cytosolic transcription activator domain, which activates the transcription of genes involved in ER quality control and the protein folding machinery (29). The role of ATF6 in cancer is yet poorly described, but this stress sensor might contribute to tumor cell dormancy and chemoresistance through the regulation of adaptive pathways (23, 30).

## IRE1 Signaling

IRE1 activity, which was first reported in relation to the splicing of *XBP1* mRNA (31–34), is now also known to be involved in the degradation of RNA (known as regulated IRE1-dependent decay, or RIDD; ref. 35), including mRNAs (36, 37), ribosomal RNA (38), and microRNAs (39, 40). In humans, IRE1 catalyzes the excision of a 26-nucleotide intron on *XBP1* mRNA, shifting the coding reading frame, resulting in the expression of a stable and active transcription factor known as XBP1s. XBP1s controls genes involved in protein folding, secretion, ERAD, and lipid synthesis (41). In addition, XBP1s forms functional dimers with ATF6f to control distinct gene-expression patterns (42). The unspliced XBP1u is suggested to play regulatory roles in (i) the efficient delivery of its own mRNA to the ER for processing and (ii) controlling the degradation of XBP1s (43). The mechanisms regulating the switch from *XBP1* splicing to RIDD activity were recently suggested *in vitro* by showing that IRE1 dimers are more active in RIDD, whereas IRE1 oligomers are responsible for *XBP1* mRNA splicing (44). This model is in agreement with previous results correlating IRE1 oligomerization with enhanced *XBP1* mRNA splicing (45). IRE1 RNase activity was also linked to its phosphorylation status at key residues (i.e., Ser724), although the other identified phosphorylation sites remain to be functionally tested (46) and, in yeast, other phosphorylation sites mediate its inactivation (47, 48). Very recently, four studies have reported the mammalian *XBP1s* mRNA ligase as the tRNA ligase RtcB (49–52). Beyond its role in *XBP1* mRNA splicing, IRE1 RNase is also involved in the direct degradation of mRNAs via RIDD. Through RIDD, IRE1 cleaves substrate RNAs, including cancer-relevant mRNAs such as *PDFGR*, *SPARC*, and *Period1* mRNA (35) and cancer-relevant microRNAs such as *miR-17* or *miR-96* (40). Finally, IRE1 activation has also been linked to the activation of the ASK1/JNK1 signaling cascade through

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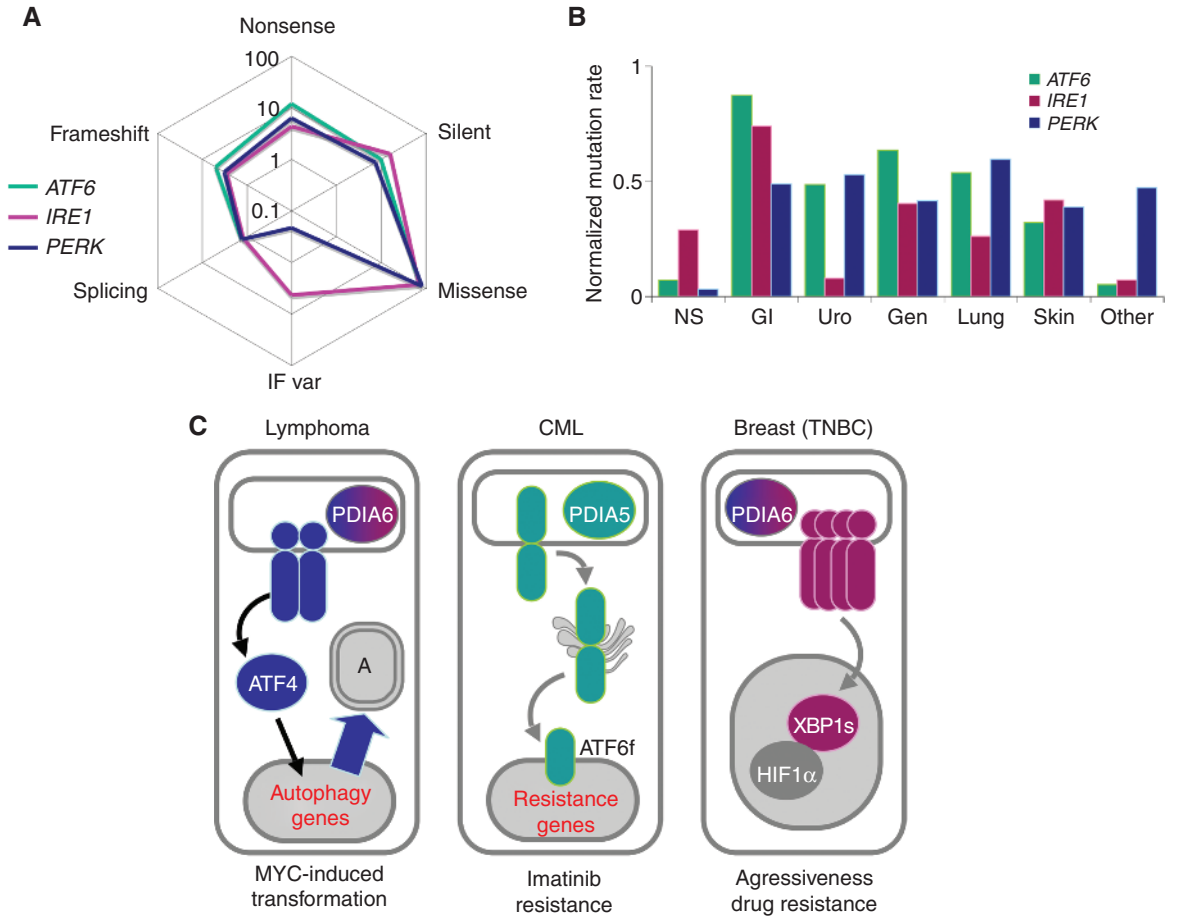


**Figure 2.** UPR sensor mutation specificity in cancer. **A,** by integrating data from the Catalogue of Somatic Mutations in Cancer (COSMIC), cBIOportal, and IntOgen databases, the spectrum of mutations found in *IRE1* (*ERN1*; purple), *PERK* (*EIF2AK3*, blue), or *ATF6* (green) was analyzed and represented according to the mutation type (missense, silent, nonsense, frameshift, splicing, or in-frame variation; IF var; deletion or insertion). **B,** similarly as in **A**, tissue distribution of the identified mutations in the three UPR sensors (same color code) was reported as normalized mutation rate integrating data from three databases (COSMIC, cBIOportal, and IntOgen) and reporting the percentage of mutations found in the total number of tumors sequenced. NS, nervous system; GI: gastrointestinal; Uro, urological; Gen, genital and gynecological. **C,** three examples of PERK-, ATF6-, and IRE1-relevant cancer signaling pathways in three different cancers, MYC-induced lymphoma, chronic myeloid leukemia (CML), and triple-negative breast cancer (TNBC). A, autophagosome.

the recruitment of TRAF2 to IRE1 (53), although this may also occur through the cleavage of *miR-17* via the control of thioredoxin-interacting protein (TXNIP; ref. 39). Altogether, these recent discoveries shed light on the complexity of the signaling mechanisms downstream of IRE1, which involve both transcriptional and posttranscriptional regulations. Moreover, these data provide more insights into the UPR-dependent biologic networks that orchestrate ER protein homeostasis (proteostasis) recovery. The understanding of how these signaling networks are altered in cancer could unravel novel and original therapeutic avenues.

## Pro-Oncogenic Potential of the Three UPR Branches

The contribution of the UPR to oncogenic processes was first proposed in 2004 (54) and is now well accepted by the community. More recently, somatic mutations have been found in genes coding for UPR sensors and reported in genome-wide sequencing studies (55). For example, three independent studies identified mutations in *IRE1* in cancers (55), including glioblastoma (56) and hepatocellular carcinoma (57). Since then, the number of cancer-associated mutations in the three UPR sensor–encoding genes has risen (Fig. 2A) and been documented in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (58). Interestingly, the somatic mutation profiles of *PERK*, *IRE1*, and *ATF6* are distinct, with missense mutations enriched in *PERK*, nonsense mutations enriched in *ATF6*, and silent mutations enriched in *IRE1* (Fig. 2A). Similarly, the spectrum of in-frame variations, splicing, or frameshift mutations was also different for the three UPR sensors, with a predominance of in-frame deletions and insertions observed for *IRE1* (Fig. 2A). The biologic causes and consequences of such mutation spectra have been partly investigated in noncancer relevant experimental systems (59); however, these mutations in UPR sensors could represent novel avenues for the selective targeting of tumors. Moreover, the incidence of mutations found in the genes encoding the three sensors also exhibited tissue specificity (Fig. 2B). Indeed, integration of mutation rates reported in three databases (COSMIC, cBIOportal, and IntOGen) revealed higher mutation rates of

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*PERK* in bone cancers ("other"; Fig. 2B). *IRE1* somatic mutations appear to be predominant in cancers of the nervous system, thereby confirming previous functional observations made in glioblastoma (60). Interestingly, *IRE1* and *ATF6* mutations are more frequently found in gastrointestinal cancers, which are most prone to exhibit mutations in the 3 UPR sensor–encoding genes (Fig. 2B). Finally, *PERK* and *ATF6* were highly mutated in urologic and lung cancers, whereas *ATF6* mutations were predominant in genital cancers. Although the biologic relevance of these mutations remains to be fully elucidated in terms of functionality (activating/inactivating, expression of the sensors, signaling specificity, and impact on tumor phenotypes), the roles of each arm of the UPR have been illustrated in several cancers (Fig. 2C). For instance, MYC-induced lymphomas require the overactivation of the PERK–ATF4 pathway and autophagy induction for complete transformation (61). This was also recapitulated in *Drosophila* models, thus pointing toward the use of such tools to decipher the underlying genetic networks (62). Moreover, overactivation of the ATF6 pathway, most likely through high expression levels of PDIA5, confers resistance to imatinib in chronic myeloid leukemia (CML) cells, and therefore inhibiting PDIs restored imatinib sensitivity (23). Finally, the IRE1 arm of the UPR, and in particular the splicing of *XBP1* mRNA, was found to be overactive in triple-negative breast cancers (TNBC), thereby conferring on these tumor cells a highly aggressive phenotype (Fig. 2C; ref. 63).

## TRANSCRIPTIONAL REPROGRAMMING BY THE UPR

The initial view of the impact of the UPR on adaptation processes directed against disturbances in ER proteostasis proposed the existence of linear pathways that control well-defined subsets of target genes, and thus unique signaling outputs. The discovery of novel functions of UPR transcription factors in the physiology of diverse organs has changed this simplistic vision, enforcing a concept where, depending on (i) the input or the stimuli (stress-dependent or stress-independent) and (ii) the cell type affected (i.e., the context: secretion-specialized cells or not), the population of target genes engaged can dramatically differ, affecting cellular functions that may not have been predicted to rely on ER stress (i.e., involved in restoring ER proteostasis; ref. 64). The selective reprogramming of gene expression by the UPR is fine-tuned, in part, by the formation of heterodimeric transcription factors, in addition to posttranslational modifications and the cross-talk of UPR stress sensors with other cancer-relevant signaling pathways. In this section, we highlight a few examples demonstrating specific mechanisms underlying the selective control of gene-expression programs by the UPR in a context-dependent manner.

### UPR Transcription Factor Networks

Gene-expression profile analysis in classic *in vitro* models of ER stress (i.e., pharmacologic perturbation to ER physiology) has suggested that most of the UPR target genes are involved in almost every aspect of the secretory pathway, including folding, quality control, ERAD, trafficking, redox control, and lipid synthesis, and in more distantly related functions such as apoptosis and autophagy (24, 65–68). Interestingly, a recent report suggested that XBP1s and ATF6f form heterodimers that drive a distinct pattern of gene expression compared with that of the respective homodimers, thereby influencing the folding, trafficking, and degradation of destabilized ER client proteins (42). The transcriptional activity of ATF6 is also determined by its binding to different cofactors and transcription factors, including NF-Y/CBF, YY1, and TATA-binding protein (TBP; refs. 25, 69, 70) and by phosphorylation (71). XBP1s is regulated by acetylation and sumoylation, in addition to phosphorylation through p38 (72–74). Similarly, ATF4 interacts with different transcription factors and is also regulated by posttranslational modifications, including phosphorylation, ubiquitination, and acetylation, which affect protein stability and thereby its availability for activating transcription (reviewed in ref. 75). A recent report assessed the regulatory network governed by ATF4 and CHOP, and indicated that these transcription factors may not occupy the promoters of genes involved in apoptosis (76). Instead, ATF4 and CHOP were shown to form heterodimers that control genes involved in autophagy and mRNA translation, which may lead to ATP depletion and oxidative stress (76). Hence, the regulation of gene expression by the UPR is complex and involves multiple dynamic mechanisms and control checkpoints.

The physiologic role of XBP1 is mostly attributed to sustaining the function and differentiation of specialized secretory cells due to their high demand for protein folding and secretion (41). A genome-wide screen to define the regulatory network under ER stress revealed that, in addition to classic secretory pathway components, XBP1s modulates the expression of a cluster of genes related to cell differentiation, DNA-repair pathways, and key genes involved in brain and muscle diseases (66). MIST1, a master regulator of cell differentiation, was identified in this study as a direct target of XBP1s, which was then functionally validated *in vivo* in the differentiation of gastric zymogenic cells (77). During B-lymphocyte differentiation, the engagement of the B-cell receptor has been proposed to regulate plasma cell differentiation through signaling events that depend on *XBP1* mRNA splicing associated with the attenuation of the transcriptional repressors IRF4 and BLIMP1 (68, 78). These studies suggest that XBP1 has relevant functions in cell differentiation that are beyond the control of protein folding stress through the modulation of well-defined gene-expression programs that when dysregulated could affect tumor cells' adaptive properties to selective environments.

Collectively, this information provides a global picture of a cancer-relevant interconnected network of UPR-activated transcription factors, which not only interact with one another but are also able to form specific complexes with other stress-relevant transcription factors (see below). These events may specifically modulate the UPR transcriptional responses and thus cancer cells' ability to cope with their altered metabolism and the challenging microenvironment.

### Transcriptional Reprogramming in Cancer Cells

Although the role of the UPR in the survival and positive selection of cancer cells in solid tumors has been well established for over a decade, a deeper knowledge of the mechanisms of action of ER stress signaling in cancer biology has only recently become available. In addition to operating as

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an adaptive mechanism to the microenvironmental changes observed in cancer, the UPR is now recognized as a relevant component that determines cell transformation and metastatic potential, in addition to its regulation of cell dormancy, genomic stability, angiogenesis, immunogenic tolerance, and the metabolic status of the cell (79). These findings have suggested that targeting the proteostasis network may be therapeutically beneficial in cancer. One of the best examples in terms of demonstrating the therapeutic potential of targeting the proteostasis network in cancer is the use of the proteasome inhibitor bortezomib for the treatment of multiple myeloma (80). Bortezomib was shown to trigger chronic ER stress, reflected in overactivation of PERK, which may sensitize cells to apoptosis (81). Recently, pharmacologic inhibitors targeting the PERK kinase domain were developed and shown to reduce pancreatic tumor growth in xenograft models (18, 19). However, as PERK plays essential roles in pancreatic beta cells' functions, the use of PERK inhibitors might have deleterious secondary effects on the organ. Interestingly, a novel compound termed ISRIB that blocks ATF4 expression (82) was recently shown to overcome the deleterious side effects of PERK inhibitors on the pancreas (83). Importantly, *in vitro* studies also indicated that bortezomib might actually inhibit *XBP1* mRNA splicing, abrogating the prosurvival consequences of this UPR signaling branch (84). This finding motivated the search for small molecules that block the RNase activity of IRE1 as a possible anticancer agent. In fact, several compounds have been identified that selectively block *XBP1* splicing (i.e., STF-083010 and MKC-3946), and have important antitumor effects in preclinical models of multiple myeloma (reviewed in ref. 85). IRE1 inhibitors also synergize with bortezomib in the killing of cancer cells. In agreement with these findings, XBP1s overactivation has been suggested to be part of the etiology of multiple myeloma, as ectopic overexpression of XBP1s in the lymphoid compartment in transgenic mice led to the spontaneous development of phenotypic alterations resembling multiple myeloma (86). This oncogenic transformation process was accompanied by the unexpected engagement of a gene-expression signature involving a variety of genes linked to the human disease, including cyclin D1, cyclin D2, MAF, MAFB, and IL6–dependent pathways.

Recent advances have highlighted the contribution of genomic reprogramming by the UPR as a determinant of cancer prognosis. XBP1s is an estrogen-regulated gene and its levels strongly correlate with estrogen receptor α expression in breast cancer (87). Consistent with this idea, XBP1 was shown to modulate estrogen receptor expression (88). A recent study of adaptive UPR responses in the absence of proapoptotic responses uncovered the induction of estrogen-dependent gene-expression signatures as a possible effect of the UPR (89). XBP1 may also control cell survival in estrogen receptor–positive cells through modulation of NFκB p65/RelA expression (90), and overexpression of XBP1 in estrogen receptor α–positive breast cancer cells can lead to antiestrogen resistance by regulating genes associated with apoptosis and cell-cycle progression (91), as well as to estrogen-induced tumor growth (87).

In addition, activation of *XBP1* mRNA splicing was recently shown to enhance the tumorigenicity and progression of TNBC cells (63) by assembling a transcriptional complex with hypoxia-inducible factor 1α (HIF1α) to regulate the expression of HIF1α target genes. As such, TNBC growth is dependent on XBP1-mediated regulation of the HIF1α transcriptional program. The gene-expression signature controlled by XBP1s in breast cancer includes VEGF, a central proangiogenic factor, as well as genes related to cell proliferation, cell growth and differentiation, cytoskeletal rearrangement, and cell survival (63). Remarkably, analysis of XBP1s-dependent gene-expression signatures in patients with TNBC revealed that this pattern highly correlated with HIF1α function and predicted poor prognosis. This finding revealed an unexpected cross-talk of the UPR with HIF1α in the reprogramming of cancer cells toward cell transformation. Although this has been proved in TNBC, *XBP1* splicing is observed in numerous cancer cell lines and tumors under unstressed conditions, but further investigation is needed to demonstrate a causal relationship with tumor aggressiveness.

High expression of XBP1 can also predict a poor outcome in pre-B acute lymphoblastic leukemia at the time of diagnosis (92), and pharmacologic inhibition of IRE1 resulted in efficient killing of pre-B lymphoblastic leukemia cells (92, 93). In these cells, XBP1 deficiency resulted in the acquisition of phenotypes that are disadvantageous for leukemia cell survival, including compromised BCR signaling capability and increased surface expression of sphingosine-1-phosphate receptor 1; this occurred most likely through the attenuation of the adaptive capacity of the secretory pathway and the subsequent impact on both intrinsic cellular metabolism and the tumor microenvironement. Similarly, high levels of XBP1s may also predict a better outcome for the treatment of multiple myeloma patients with bortezomib, most likely through an established addiction to the signals mediated by this transcription factor (94, 95).

In summary, accumulating evidence suggests that the UPR is a relevant driver of oncogenic transformation that could be used for prognosis. Measuring XBP1-dependent and XBP1-independent gene-expression responses may serve as a biomarker to predict the evolution of disease progression. It remains to be determined if similar observations are recapitulated with ATF4 and ATF6.

## Tumor Microenvironment and ER Stress

An acquired feature of malignant cells is the ability to rewire their metabolism to support sustained growth (96). Indeed, the nutrient requirements eventually exceed the capacity of the cells' microenvironment due to inadequate vascularization, thus leading to hypoxia and nutrient limitation. To survive these environmental stresses, tumor cells induce adaptive responses, including the UPR (54). The UPR has critical functions beyond adjusting proteostasis. For example, the PERK–ATF4 branch upregulates VEGF to induce angiogenesis (97). Moreover, it is now becoming clear that the UPR can directly participate in the reprogramming of tumor metabolism by selectively activating biosynthetic pathways. Indeed, it is well established that ER stress signaling pathways control protein synthesis, folding, and degradation machineries (98). This is illustrated by the direct regulation of protein synthesis through PERK-mediated phosphorylation of eIF2α (99), IRE1-mediated RNA degradation (35), and control of the expression of ER proteins involved in folding or degradation (98). Changes in proteostasis have been associated with tumor-associated gains-of-function that can be reversed

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using proteostasis modulators such as proteasome inhibitors that overcome the adaptive capacity of the UPR and induce cell death (85). The PERK–ATF4 branch is also known to regulate catabolic pathways such as autophagy through ATF4-dependent induction of autophagy genes (100) and to modulate amino acid and lipid metabolism, again through ATF4-mediated induction of select targets.

In the tumor microenvironment, XBP1s is part of a response that mediates the transcriptional induction of UDP-galactose 4-epimerase to generate substrates for protein glycosylation, thereby coping with the increased protein folding and post-translational demand in tumor cells (101). In addition, the constitutive splicing of *XBP1* drives tumorigenicity by assembling a transcriptional complex with HIF1α, which activates a transcriptional program that upregulates glycolytic proteins, including glucose transporter 1 (GLUT1; ref. 63). XBP1 also controls the expression of the hexosamine biosynthetic pathway (102) and negatively regulates the levels of the transcription factor FOXO1, thereby affecting energy control and glucose metabolism, both controlled by genes dependent on FOXO1-mediated transcription (103) as well as ER homeostasis (104, 105). This provides a potentially cancer-relevant link between IRE1 and PERK signals, as both stress sensors can regulate the functionality of FOXO transcription factors (16). These studies indicate that XBP1s actively promotes the stimulation of glucose uptake by cancer cells. Notably, XBP1 appears to have more than one effector to ensure the same biologic output, namely cancer cell adaptation to intrinsic demand and/or extrinsic challenges.

In addition, accumulating evidence suggests that the UPR signaling network is associated with other cancer-relevant signaling pathways and modulates the activity of various transcription factors (i.e., c-JUN, MAPK, CREB, NRF2, HIF1α, NFκB, mTOR, and AKT) to generate distinct gene-expression patterns associated with tumor phenotypes, including aggressiveness or angiogenesis (reviewed in ref. 43). Thus, it is predicted that, in cancer cells, therapeutic targeting of the UPR may have unpredicted effects (i.e., independent of protein misfolding in the ER) beyond protein folding stress that may depend on the transformed cell type (i.e., secretory capacity of the cell, nature of the oncogenic stimulation, and stage of the transformation).

In addition, in order to generate additional energy supply under environmentally induced starvation, cancer cells also have the capacity to trigger ER stress–dependent autophagic pathways. As such, the PERK–eIF2α–ATF4 pathway is activated upon hypoxia in tumor cells (9) and protects these cells from environmental damage (106) through autophagy via LC3B and ATG5 (107). Similarly, a link was established between IRE1 signaling and autophagy induction through the binding of TRAF2 to IRE1 and the downstream activation of JNK (108). This pathway is repressed under nutrient starvation conditions by the ER-located protein BI-1/TMBIM6 (102), a negative regulator of IRE1 (103) that plays an essential role in numerous cancers (109, 110). Thus, it is easily conceivable that, as for PERK, IRE1 might represent a significant player in the control of autophagy in response to environmental challenges. In addition, genetic inactivation of *XBP1* has been shown to switch the proteostasis network toward autophagy upregulation, which could generate adaptive advantages by (i) actively removing proteotoxic aggregates caused by the imbalance between the protein folding demand and the protein folding capacity of the tumor cell, and (ii) providing nutrients through catabolic processes and therefore compensating for environmental nutrient starvation (111). These studies illustrate a highly dynamic network that controls cancer cells' ability to adapt and resist environmental stresses through UPR-dependent mechanisms.

## ER Stress and DNA Damage/Repair

Although less explored, recent evidence suggests that ER stress may also affect genomic stability and DNA-repair pathways, which may contribute to oncogenic transformation. Bidirectional regulation between the UPR and DNA-damage responses has been shown in various experimental systems (112–116), suggesting a dynamic feed-forward homeostatic regulation that controls the stability of the proteome and genome. Studies in yeast uncovered a relevant function of IRE1p in maintaining the stability of the genome (117, 118). IRE1p deficiency led to chromosome loss under basal conditions, a phenomenon that was further enhanced when DNA damage was generated by UV exposure. Although these findings have not been validated in mammalian cells, global assessment of the XBP1s regulatory network identified a cluster of DNA-damage and DNA-repair genes as direct targets of XBP1, as mentioned above (66). However, the functional contribution of these genes to the ER stress response is unknown. A better understanding of why and how ER stress signals control DNA–damage/repair pathways and the impact this cross-talk could have in cancer is therefore required.

ATM-deficient cells undergo hyperactivation of IRE1 when exposed to ionizing radiation (119), and both p53-deficient cells and ATM-deficient cells develop spontaneous alterations in ER proteostasis (119–121). Cross-talk between the UPR and p53 has been reported in many studies (see examples in refs. 122–125), which may influence gene expression toward cell adaptation or induction of apoptosis, and thus determine cancer cell fate. For example, a recent report provided evidence suggesting that UPR signaling modulates the function of a p53 isoform (122). In addition, ER stress may affect the cell cycle and protein translation in a p53-dependent manner (123, 124). p53 is also a relevant mediator of ER stress–dependent apoptosis through the transcriptional upregulation of the BCL2 family members PUMA and NOXA (125), and, interestingly, p53-deficient mice exhibit constitutive ER stress (120).

Genetic inactivation of *PERK* also results in genomic instability, possibly due to uncontrolled ROS production (126), most likely through a signal emanating from the mitochondrial associated membranes (MAM; ref. 127), and cross-talk between PERK signaling and DNA-repair pathways has been reported (128). Finally, genomic instability associated with the generation of tetraploid cells involves basal levels of ER stress, with exposure of the ER chaperone calreticulin at the cell surface contributing to immunogenic cell death—again, this could occur through the roles played by PERK in MAMs—and thus regulating intracellular calcium fluxes and ROS production (129). In summary, these studies suggest a link between ER stress signaling and DNA–damage/repair mechanisms involving, in part, p53. Although this subject is predicted to have high relevance for cancer cell proteostasis, as illustrated by the increasing number of reports linking protein homeostasis to transcriptional and genome maintenance

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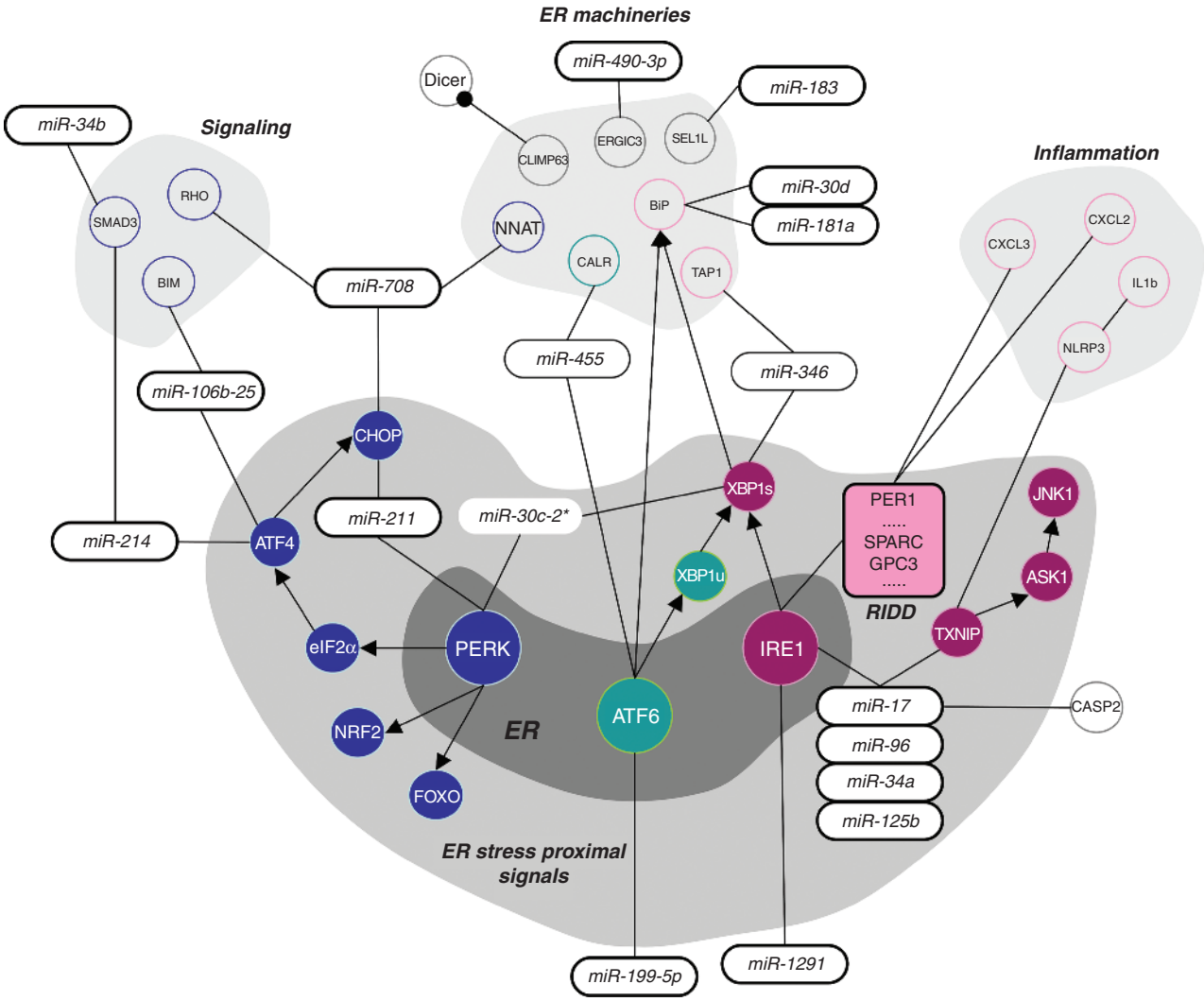


**Figure 3.** UPR-mediated posttranscriptional and posttranslational networks in cancer. The three UPR sensor pathways depending on PERK, ATF6, and IRE1 are respectively represented in blue, green, and purple. MicroRNAs with direct evidence of a link to cancer are circled in bold, those with indirect evidence are circled, and those with no evidence are not circled.

events (130, 131), further functional studies are required for validation in cancer models in *vivo*.

## ER STRESS–MEDIATED POSTTRANSCRIPTIONAL SIGNALING NETWORKS

Posttranscriptional regulation represents a significant mechanism by which the UPR influences cancer development. This phenomenon can be achieved through either the direct degradation of select mRNAs or modulation of the expression of posttranscriptional regulators, such as microRNAs. Indeed, noncoding RNAs have been described to positively or negatively affect the ER stress response (Fig. 3) either through specific targets or through yet unclear mechanisms.

### MicroRNAs and ER Stress in Cancer

miRNAs have been shown to influence apoptosis induction under ER stress through different targets. For example, overexpression of the *miR-23a~27a~24-2* cluster upregulates proapoptotic components such as CHOP, TRIB3, ATF3, and ATF4 (132). Other miRNAs can modulate the amplitude of UPR signaling, including *miR-122*, which represses ER stress signals in hepatocellular cancers through a CDK4–PSMD10 pathway (133), and *miR-214*, which promotes ATF4 downregulation (134) and targets XBP1 expression through a yet unclear mechanism (135). Reciprocally, ER stress suppresses the expression of the *miR-199a/miR-214* cluster in hepatoma cells through an NFκB-dependent pathway (135), suggesting that the *miR-199a/miR-214* cluster might represent an example of miRNAs as both regulators and effectors of the UPR. In addition, *miR-708* expression is controlled by CHOP and contributes to brain metastasis (136). PERK signaling has been shown to regulate the expression of miRNAs involved in the subsequent modulation of the UPR. For example, repression of the *miR-106b-25* cluster by PERK signaling is required for the induction of BIM and apoptosis during ER stress (137). Moreover,

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PERK activation also promotes the expression of *miR-30-c-2**, which represses the expression of XBP1 (138), and *miR-211*, which results in ER stress–dependent attenuation of CHOP expression (139). These examples illustrate how miRNA-dependent signaling circuits are tightly regulated downstream of the UPR (Fig. 3). Collectively, these observations point toward an additional layer of complexity in the orchestration of the ER stress response, allowing for the tight control of selected transcriptional programs that regulate not only the survival/death balance but also other specific tumor features (i.e., invasion/migration or control of the tumor stroma).

### ER Stress–Dependent RNA Stability in Cancer

RNA degradation upon ER stress has been described to occur through nonsense-mediated RNA decay (NMD; ref. 140) and through RIDD (35). NMD is an mRNA quality-control mechanism known to destabilize aberrant mRNAs that contain premature termination codons. NMD was recently shown to determine the threshold of stress necessary to activate the UPR, in addition to adjusting the amplitude of downstream responses and the termination phase. These effects were mapped to the control of the mRNA stability of *IRE1*, highlighting the dynamic cross-talk between mRNA metabolism and the proteostasis network. Although NMD has not yet been linked directly to cancer development, RIDD has been illustrated to be involved in tumor-specific phenotypes in several instances. In gliobastoma, IRE1-mediated decay of the circadian regulator Period1 was shown to increase tumor inflammation and infiltration properties, most likely through the secondary transcriptional regulation of gene expression (60). Moreover, in the same type of tumors, IRE1 was identified to cleave *SPARC* mRNA, thereby leading to changes in the collective versus individual migration of glioblastoma cells and reducing cell migration (141). The pro-oncogenic glypican-3 (*GPC3*) was also identified as a substrate of IRE1 RNase in hepatocellular carcinoma (Fig. 3; ref. 142). These studies provide clues about the possible contribution of IRE1 inactivation through genetic mutation in cancer; however, even though IRE1 appears globally to act as a prosurvival factor in cancer, the precise underlying mechanisms remain to be fully characterized, and one might also predict that the different enzymatic activities of this protein (kinase/RNase) and substrate selectivity (mRNA, *XBP1*, rRNA, or miRNA) will affect tumor and stromal cell fate.

A systematic analysis of RIDD substrates in different cancer models therefore becomes necessary to identify the relevant networks to possibly be either genetically or pharmacologically targeted and to clarify the mechanisms involved in cell death signaling driven by IRE1 (reviewed in ref. 143). RIDD activity increases proportionally with ER stress intensity, inducing the degradation of mRNA substrates required for cell survival and cell growth and thus leading to cell death (35). For example, RIDD induces the decay of several miRNA precursors, such as that of *miR-17* (40), which represses the expression of the pro-oxidant TXNIP that contributes to the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome (39). The decay of pre–*miR-17* by RIDD increases TXNIP expression, NLRP3 inflammasome activation, and the subsequent cleavage of pro–caspase-1 and secretion of IL1β, thereby inducing systemic or local inflammatory responses and promoting cell death (Fig. 3; ref. 39). In addition, the cleavage of pre–*miR-17* by IRE1 was found to derepress caspase-2 expression and promote ER stress–induced apoptosis (40). However, the contribution of caspase-2 to UPR-mediated cell death remains unclear (144). *miR-17* is the only validated miRNA whose expression has been shown to be directly regulated by IRE1-mediated cleavage (40), and has been shown to be involved in tumor aggressiveness in gliobastoma (145), hepatocellular carcinoma (146), and prostate (147), kidney (148), gastric (149), and colon (150) cancers. However, IRE1 has also been implicated in the degradation of other pre-miRNAs that are involved in cancer development, such as *miR-96*, whose overexpression has been observed in bladder (151), prostate (152), and breast (153) cancers and has been shown to possess tumor-suppressor functions in pancreatic cancer (154). Overall, because RIDD targets are thought to depend on the cellular context (abundance of the respective substrates in a given cell type), the stimuli engaging IRE1 (nature of the UPRosome formed as well as size of the oligomers), and the presence of somatic mutations altering IRE1 conformation, we predict that this specific output of the UPR, together with the expression of classic ER stress transcription factors, will drive distinct gene-expression patterns that affect multiple aspects of cancer biology, including control of (i) the tumor cell death/survival balance, (ii) tumor cell invasion and metastasis properties, and (iii) the nature of the tumor stroma.

## CONCLUSION

Over the past decade, we have witnessed major advances in our understanding of the contribution of the UPR to oncogenesis and the acquisition of chemoresistance in cancer cells. There are now many new open questions that need to be addressed with regard to the role of the UPR in cancer. Two key problems to be solved are "when is a stress too much?" and "what is the quantitative contribution of specific ER stress signaling modules during malignant transformation?" Indeed, many cancer cells die during transformation, tumor formation, and metastasis due to their inability to cope with the combined oncogenic and microenvironmental stresses. However, tumors that develop following the selection process often have a high basal UPR and, in particular, high IRE1 or PERK activities. Although this high basal UPR activity confers a survival advantage to the tumor cells, it also keeps the cells on edge, so that either dampening the UPR response (e.g., by inhibition of different arms of the UPR) in the face of the continued stress signals or increasing stress levels (e.g., administration of chemotherapy) will tip the balance in favor of cell death. One could also anticipate different roles played by each arm of the UPR at distinct stages of tumor progression, including (i) initial stages of oncogene-induced cell transformation, (ii) tumor vascularization, (iii) metastasis, including extravasation, (iv) survival in the blood flow and then (v) intravasation and growth in the host niche.

Another question that is linked to the focus of this review is what determines the switch between prosurvival and prodeath UPR signals? This is an area of much interest, as the answer to this question should allow the development of novel drugs that selectively tip the balance in favor of prodeath UPR signals as an anticancer therapeutic strategy. However,

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evidence to date suggests that the mechanisms underlying cell fate control under ER stress are unlikely to be so simplistic and that a greater understanding of the UPR under different ER stress–inducing conditions (i.e., oncogene expression, nutrient deprivation) and in different cellular contexts (i.e., tumor cell type or subtype) is needed to predict how UPR-targeting drugs might affect tumor growth and progression. In particular, a better understanding of the UPR itself is needed, in addition to its integration with other signaling pathways and how it relates to cell fate control. Such an understanding would pave the way for personalized treatment of cancer based on a patient's tumor cell type and the activation status of UPR-related signaling networks.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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