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The Impact of the ER Unfolded Protein Response on Cancer Initiation and Progression: Therapeutic Implications

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Abstract

Cellular stress induced by the accumulation of misfolded proteins in the endoplasmic reticulum (ER) activates an elaborate signalling network termed the unfolded protein response (UPR). This adaptive response is mediated by the transmembrane signal transducers IRE1, PERK, and ATF6 to decide cell fate of recovery or death. In malignant cells, UPR signalling may be required to maintain ER homeostasis and survival in the tumor micro-environment characterized by oxidative stress, hypoxia, lactic acidosis and compromised protein folding. Here we provide an overview of the ER response to cellular stress and how the sustained activation of this network enables malignant cells to develop tumorigenic, meta-static and drug-resistant capacities to thrive under adverse conditions. Understanding the complexity of ER stress responses and how to target the UPR in disease will have significant potential for novel future therapeutics.

Keywords

ATF6; Oxidative stress; ER stress; UPR; IRE1α; XBP1; ATF4; PERK; Cancer; BiP; Chaperones

8.1 Adaptive Signalling for Endoplasmic Reticulum (ER) Protein Homeostasis

The endoplasmic reticulum (ER) is a highly dynamic stress-sensing organelle essential for cellular homeostasis that integrates different extracellular and intracellular stimuli to coordinate downstream translational and transcriptional responses. The ER is a major platform for secretory protein homeostasis, or proteostasis, that consists of the coordinated folding, processing and trafficking of at least a third of the proteome, coupled to quality control mechanisms. Understanding how cells ensure the conformational integrity of their proteome when challenged with acute and chronic stress is fundamental to health and

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disease. Research in the past decades has helped unravel the complexity of protein folding and revealed that aberrant folding and aggregation of proteins can lead to disease.

8.2 ER Protein Folding and Quality Control Mechanisms

The life cycle of a protein begins as a linear sequence of amino acids extending from the 80S ribosome. Proteins destined for intracellular organelles and secretion are co- or post-translationally translocated across the ER membrane in an unfolded state. The folding of a polypeptide in the ER allows it to acquire its native conformation and associated post-translational modifications and is often facilitated by ER resident chaperones such as immunoglobulin binding protein (BiP/GRP78), calnexin and calreticulin and enzymes including protein disulfide isomerases (PDIs) and *cis-trans* peptidyl-prolyl isomerases (PPIs). Correctly folded proteins are then transported to the Golgi compartment and subsequently sorted for trafficking to their ultimate cellular destination.

Due to the complexity of protein folding, it is the most error-prone step in gene expression (Wang and Kaufman 2016). As a result, quality-control machines engage terminally misfolded proteins for ER-associated degradation (ERAD) and/or autophagy to selectively degrade the mis-folded protein or to activate the unfolded protein response (UPR). The UPR is an adaptive mechanism that re-establishes proteostasis in the ER. However, if the adaptive UPR is overwhelmed by chronic or severe ER protein misfolding and is unable to preserve ER function, the UPR activates an apoptotic response. It is believed that apoptotic cell death prevents release of misfolded non-functional proteins from the cell.

8.3 The Unfolded Protein Response (UPR)

When misfolded proteins accumulate in the ER, the cell engages the UPR to increase the ER protein-folding capacity for its needs (Fig. 8.1). The UPR is a conserved signalling network evolved to restore ER homeostasis and in metazoans involves the activation of three transmembrane sensors: (i) inositol-requiring enzyme 1 (IRE1); (ii) PKR-like ER kinase (PERK); and (iii) activating transcription factor 6 (ATF6). These ER-localized UPR signal transducers convey information about the intensity and duration of the stress stimuli through the detection of mis-folded proteins in the ER and signal to the cytosol and nucleus to either restore proteostasis or induce apoptosis. Under unstressed conditions, IRE1α, PERK and ATF6 are maintained in inactive states by interaction with the luminal ER chaperone BiP. During ER stress, BiP binds to misfolded proteins promoting dissociation from the ER stress sensors, thereby permitting their activation to induce selective protein synthesis attenuation and gene transcription.

8.4 IRE1α

IRE1α is the most conserved UPR transducer, possessing catalytic serine/threonine kinase and endoribonuclease (RNase) activities. Following BiP dissociation from its ER luminal N-terminal domain, IRE1α dimerizes and oligomerizes while stimulating *trans*-autophosphorylation, inducing a conformational change that activates the cytosolic RNase domain (Han et al. 2009; Korennykh et al. 2009; Lee et al. 2008). Recent evidence also suggests that unfolded proteins may be sensed by binding directly to IRE1α and inducing an allosteric change that triggers IRE1α activation (Karagoz et al. 2017). Once ER protein homeostasis is restored, IRE1α oligomers disassemble concomitantly with IRE1α dephosphorylation to return to a basal IRE1α monomeric inactive state bound to BiP (Karagoz et al. 2017).

Activated IRE1α initiates the unconventional splicing of the mRNA encoding the X-box binding protein 1 (XBP1) and the regulated IRE1α- dependent decay (RIDD) (Han et al. 2009; Hollien and Weissman 2006; Hollien et al. 2009) of mRNAs and miRNAs. Spliced XBP1 (XBP1s) induces expression of genes that encode ER protein folding, secretion, ERAD and lipid synthesis functions (Hetz et al. 2011). Physiological RIDD activity appears to be an ancestral mechanism to ensure ER homeostasis by reducing the protein folding burden, while hyperactivated RIDD is associated with an apoptotic cellular output (Maurel et al. 2014). The mechanism controlling the switch from cytoprotective to cytotoxic RNase function remains to be identified, although it may involve oligomerization of activated IRE1α molecules (Han et al. 2009).

The IRE1α platform for signalling is described as a dynamic scaffold termed the "UPRosome" onto which regulatory components assemble to orchestrate crosstalk between the UPR and other signalling pathways (Hetz and Glimcher 2009). The direct binding of the ER chaperone HSP47 (Sepulveda et al. 2018), ERdj4/DNAJB9 (Amin-Wetzel et al. 2017), and the ER resident ER protein disulfide isomerase PDIA6 (Eletto et al. 2014; Groenendyk et al. 2014) to IRE1α may modulate its signalling behaviour. The recruitment of TRAF2 can also trigger JNK or NFκB activation, which may participate in the regulation of insulin resistance, inflammation and apoptosis (Marciniak and Ron 2006; Urano et al. 2000). IRE1α signalling may further be activated by pro-apoptotic BCL2 members BAX and BAK (Hetz et al. 2006), or negatively regulated by BI-1 (Bailly-Maitre et al. 2010; Lebeaupin et al. 2018b; Lisbona et al. 2009). Hence, the assembly of distinct adaptors and modulators on the cytosolic or luminal domains of IRE1α fine-tunes downstream signalling (Hetz et al. 2015). The physiological significance of these interactions remains to be explored.

8.5 PERK

During the early phase of ER stress, PERK is acutely activated to phosphorylate the heterotrimeric GTPase eukaryotic translation initiation factor 2 on the alpha subunit (eIF2α) at Serine residue 51 (Ser51) to attenuate protein synthesis and reduce the load on the ER to support protein folding (Kaufman 2004). Phosphorylated eIF2α halts the initiation of mRNA translation, while paradoxically increases the selective translation of numerous mRNAs that have upstream open reading frames (uORFs) in their 5′ untranslated region, including *Atf4, Chop* and *Gadd34* (Blais et al. 2004; Harding et al. 1999). The transcription factor ATF4 transactivates a cluster of UPR target genes involved in amino acid synthesis and transport, protein synthesis and folding, autophagy, redox homeostasis, and apoptosis (Cullinan et al. 2003; Han et al. 2013; Harding et al. 2003). In particular, ATF4 induces expression of C/EBP homologous protein (CHOP) (Averous et al. 2004) and GADD34 that mediates eIF2α dephosphorylation and restores global mRNA translation (Ma and Hendershot 2003; Novoa et al. 2001). ATF4 may form heterodimers with CHOP, and transcriptional induction through ATF4 and CHOP leads to increased protein synthesis that causes oxidative stress and cell death (Han et al. 2013). Although it was originally proposed that PERK directly regulates redox homeostasis through phosphorylation of nuclear factor E2-related factor 2 (NRF2) to cause dissociation from KEAP1 permitting it to increase antioxidant gene expression, the physiological significance of this is yet to be demonstrated (Cullinan and Diehl 2004; Cullinan et al. 2003).

8.6 ATF6

ATF6 is synthesized as a type II ER-resident transmembrane protein bearing a large cytosolic N-terminal B-Zip transcriptional activation domain. Upon accumulation of unfolded proteins, ATF6 is released from BiP for trafficking to the Golgi apparatus for cleavage by the Golgi-resident proteases S1P and S2P, generating a cytosolic fragment that migrates to the nucleus to induce UPR target genes encoding functions in protein folding and ERAD (Haze et al. 1999; Nadanaka et al. 2004; Shen et al. 2002; Wu et al. 2007).

Together, the three main UPR pathways lead to activation of the major transcription factors XBP1s, ATF4, CHOP and ATF6 that govern the expression of a large range of genes encoding overlapping functions, creating a dynamic UPR network. Under conditions of chronic or severe ER stress, these UPR signalling pathways play critical roles in disease pathogenesis.

8.7 The ER Response to Cellular Stress

Despite the robustness of the ER, cells remain susceptible to various intracellular and extracellular insults that compromise protein folding or exert additional demands on the secretory path-way. Inefficient protein trafficking to the Golgi and the accumulation of misfolded proteins in the ER are responsible for the development and progression of many diseases. For example, Factor VIII expression, which is defective in the coagulation disorder hemophilia A, is limited due to unstable mRNA, polypeptide interaction with ER chaperones and inefficient transport of the primary translation product from the ER to the Golgi (Miao et al. 2004; Pipe et al. 2001). Moreover, the hallmark of many neurodegenerative diseases is the accumulation of protein aggregates. Understanding the causes of protein misfolding, protein aggregation and protein quality control is critical to developing novel therapeutic strategies for intervention in diseases of protein misfolding.

8.8 Oxidative Stress and ROS Production

Cellular stress can arise from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms that lead to organelle dysfunction. Disulfide bond formation, mediated by ER oxidases (ERO1s) and protein disulphide isomerases (PDIs), can alter the redox status of the ER (Tu and Weissman 2004). Oxidative protein folding, detoxification and mitochondrial respiration are all processes that generate ROS such as the superoxide radical (O_2-) and hydrogen peroxide (H_2O_2). If produced in excess, ROS lead to oxidative stress that damage proteins, lipids and DNA to alter cellular function and architecture and induce apoptosis (Cao and Kaufman 2014). The major pro-apoptotic factor of the UPR, CHOP, activates ERO1α transcription leading to increased ROS production and Ca^{2+}-dependent apoptosis through inositol trisphosphate receptors (IP_3R) (Li et al. 2009). Ca^{2+} released from the ER is taken up by mitochondria, which subsequently opens the permeability transition pore to release cytochrome c and activate the caspase cascade of apoptosis. Recently, IRE1α was found to physically interact with IP_3R and control mitochondrial Ca^{2+} uptake at mitochondrial-associated membranes (MAMs) (Carreras-Sureda et al. 2019).

To protect against the deleterious impact of oxidative stress, antioxidant responses exist to restore cellular redox homeostasis. Certain antioxidant genes (*Ngf*, *Ho-1*, *Txnrd1*, *xCT*, *p62*) may be enhanced by NRF2 and ATF4 cooperation (Mimura et al. 2019). Nevertheless, in pathological conditions the antioxidant response may be impaired.

8.9 Cell Death Pathways Ensuing Prolonged or Severe ER Stress

Over the past thirty years, two fundamental mechanisms by which cells die in response to ER stress were discovered: (1) ER stress directly causes oxidative stress leading to cell death (Back et al. 2009; Han et al. 2015; Malhotra et al. 2008; Song et al. 2008); and (2) Chronic ER stress paradoxically increases protein synthesis leading to proteostatic stress that causes cell death (Back et al. 2009; Han et al. 2013; Nakagawa et al. 2014; Song et al. 2008).

There is ample experimental evidence indicating that misfolded protein accumulation in the ER causes oxidative stress generated by the mitochondrial electron transport chain (ETC), and the intimate functional cooperation between ER and mitochondria is likely causal for such an observation. Mitochondria provide ATP to the ER which is essential to support ATP-dependent protein chaperone functions, such as BiP/GRP78 (Dorner et al. 1990), for protein folding and trafficking. In fact, the level of cellular ATP determines which proteins are able to transit to the cell surface (Dorner et al. 1990, 1992). In response, the ER signals mitochondria to stimulate ATP production through ER-to-mitochondria Ca^{2+} trafficking. ER stress is associated with increased Ca^{2+} trafficking through IP_3Rs on the ER membrane to enter the mitochondrial matrix (Carreras-Sureda et al. 2019; Kaufman and Malhotra 2014; Luciani et al. 2008; Yong et al. 2019). Although ER Ca^{2+} release channels have been known for decades and are relatively well-characterized (La Rovere et al. 2016), only recently has the mitochondrial Ca^{2+} uniporter (MCU) (Kwong 2017; Kwong et al. 2015; Pan et al. 2013) and the associated regulatory molecules been identified (Liu et al. 2016; Mallilankaraman et al. 2012; Sancak et al. 2013; Waldeck-Weiermair et al. 2015). Irrespective of the mechanism, Ca^{2+} trafficking from ER to mitochondria potentiates oxidative phosphorylation by activating NADH dehydrogenases (Kaufman and Malhotra 2014), which may further increase mitochondria-derived ROS production. *In vivo*, we hypothesize that a process of IP_3R-mediated Ca^{2+} release, in response to IP_3 generating hormonal receptor engagement, exacerbates ROS production due to mitochondrial Ca^{2+} overload. Supporting such a scenario, cardiomyocyte-specific *Mcu* deletion was protective in acute ischemia-reperfusion injury models (Kwong 2017; Pan et al. 2013).

Among the UPR transducers and downstream signalling molecules, the PERK-P-eIF2α path-way is intimately involved in mediating both cellular survival and death. Activated

PERK phosphorylates eIF2α at Ser51, leading to rapid, reversible inhibition of mRNA translation initiation. PERK mutation in humans, and mice, is the cause of infantile onset diabetes associated with Wolcott-Rallison syndrome (Delepine et al. 2000). Experimentally, a Ser51 to Alanine (Ser51Ala) mutation introduced into the endogenous murine *eIF2α* gene generated mice that cannot phosphorylate eIF2α (Scheuner et al. 2001). Homozygous Ser51Ala mutant mice die perinatally due to hypoglycemia and defective hepatic gluconeogenesis. When fed a high fat diet (HFD) that triggers insulin resistance, heterozygous Ser51Ala mutant mice develop pancreatic β-cell failure and overt diabetes (Scheuner et al. 2005). In addition, since β-cell failure due to eIF2α-S51A mutation recapitulates all the effects of PERK deletion in mice and humans (Back et al. 2009), the findings support the model where PERK acts through P-eIF2α to attenuate protein synthesis (mainly proinsulin) and translocation into the ER, and thereby limits ER stress-induced β-cell death. Importantly, in the setting of increased proinsulin misfolding, CHOP protein, controlled primarily via the PERK branch of the UPR pathway contributes to β-cell death associated with unsuppressed protein synthesis and increased ROS production (Han et al. 2013; Song et al. 2008). Curiously, without ER stress, sole expression of CHOP does not promote cell death, *in vitro* or *in vivo* (Han et al. 2013; Southwood et al. 2016; Wang et al. 1998). Furthermore, ChIP-Seq and mRNA-Seq did not reveal any death-promoting genes directly transcriptionally activated by CHOP (Han et al. 2013). Instead, the death-promoting effect by CHOP expression in the context of ER stress was shown to be a consequence of increased protein synthesis in stressed cells, thereby further promoting oxidative stress leading to irreparable cellular damage (Han et al. 2013; Marciniak et al. 2004; Song et al. 2008). These observations suggested that the notorious “death- promoting” role of CHOP is more accurately attributed to its transcriptional role as a master regulator of ER-oriented anabolic metabolism (Yong et al. 2016). Indeed, deletion of the *Chop* gene delays the onset of hyperglycemia in the *Akita* mouse (Oyadomari 2002) and suppresses β-cell failure in response to insulin resistance in diet-induced obese mice and the leptin receptor mutant *db/db* mice (Song et al. 2008). The significance of ROS production was demonstrated by showing that antioxidant feeding prevents β-cell death in response to ER stress (Back et al. 2009; Han et al. 2015; Hassler et al. 2015; Malhotra et al. 2008).

To summarize the role of PERK branch in the UPR, although other factors (such as inflammation pathways) are proposed to cause cell failure, analysis of mice with *eIF2α* Ser51Ala mutation or *Perk* gene deletion supports the notion that increased protein synthesis is sufficient to generate ROS through ER-to-mitochondria crosstalk (Kaufman and Malhotra 2014; La Rovere et al. 2016) that initiates cell death.

8.10 ER Stress in Tumorigenesis

UPR activation is documented in many cancer types (Wang and Kaufman 2014) (Fig. 8.2). Accumulating evidence supports the notion that UPR signalling is integral to cell transformation and tumor progression, although the mechanisms remain poorly defined. As discussed above, protein misfolding in the ER is sufficient to cause oxidative stress (Nakagawa et al. 2014), and it was proposed that ER stress-induced oxidative stress may damage DNA, and further cause somatic gene mutations (Shalapour et al. 2017), further leading to oncogene activation or tumor suppressor gene inactivation. However, once a tumor microenvironment forms, the transformed cells likely depend on UPR signalling to promote cell growth under the unfavorable conditions of the microenvironment, e.g. hypoxia, nutrient deprivation (Milani et al. 2009; Mujcic et al. 2013; Rouschop et al. 2013; Rzymski et al. 2009), and to evade immune surveillance by the adaptive immune response.

8.11 ER Stress and UPR Activation in Cancer Cells

It is incompletely understood how ER homeostasis is perturbed in cancer cells, and how UPR signalling can impact tumorigenesis. After an initiating tumorigenic event, the UPR is likely essential to protect cells from ER stress-induced cell death and thereby promotes cancer progression. Under this scenario, UPR signalling may be required to maintain ER homeostasis to prevent ROS accumulation incurred from cancer cell damage and apoptosis. For example, previous studies demonstrated a severe hypoxic microenvironment activates the PERK-eIF2α arm of the UPR, leading to increased glutathione synthesis and consequently protection against ROS produced during periods of hypoxia, which is believed to contribute to therapy-resistance of cancer cells (Rouschop et al. 2013). Epithelial-to-mesenchymal transition (EMT) and the secretory-associated senescence phenotype (SASP) are cellular processes associated with metastasis and require increased protein secretion of cytoskeletal matrix proteins, metalloproteases and growth factors. The increased secretion can activate the UPR and thus prime the cells for preferential death upon pharmacological induction of the UPR (Denoyelle et al. 2006; Feng et al. 2014).

Cancer cells experience ER stress as identified by high level expression of UPR biomarkers (e.g., BiP/GRP78, CHOP, XBP1s and TRIB3). Some of these proteins provide protective and adaptive functions for survival of the cancer cell; most notably elevated BiP expression correlates with increased tumor grade (Dong et al. 2011). Alternatively, some of the UPR induced genes, most notably *Chop*, promote cell death. Due to the increased sensitivity of tumor cells to ER stress it may be possible to pharmacologically activate the UPR to kill tumor cells. Targeting the UPR may provide tumor-selective killing because normal cells, without basal ER stress, can mount an adaptive UPR and return to homeostasis. The majority of efforts to target the UPR in cancer are directed at compounds that activate the pro-apoptotic UPR (Flaherty et al. 2013, 2014) and will be discussed below.

8.12 The Role of IRE1 and XBP1s in Cancer

An early study discovered that IRE1α (*Ern1)* ranked 5th among 518 protein kinase genes that carry at least one driver mutation (Greenman et al. 2007), although it is unknown whether these mutations cause a gain or loss of function. In the same pathway, XBP1s was reported to drive multiple myeloma (Carrasco et al. 2007). IRE1α and XBP1 loss of function mutations were identified in tumor cells from multiple myeloma patients that were resistant to proteasome inhibitors (Hong and Hagen 2013; Leung-Hagesteijn et al. 2013). Inactivation of the IRE1α/XBP1s pathway reduced immunoglobulin (IgG) gene expression so the plasma cells dedifferentiated to preplasma-blasts that were resistant to proteasome inhibition because they did not express IgG which misfolds in the ER lumen. Furthermore, XBP1 splicing was suggested to cause human triple negative breast cancers, in part through its proposed role by increasing HIF1α expression (Chen et al. 2014). Increased XBP1s expression in luminal breast cancer mediates resistance to anti-hormonal therapy by stimulating Nuclear Receptor Coactivator 3 (NCOA3) (Gupta et al. 2016). Moreover, increased XBP1 expression is commonly observed in patients with acute myeloid leukemia (~70%) and leukemia cell lines (Sun et al. 2016). Along the same line, knocking-down XBP1 expression levels increased the susceptibility of multiple myeloma cells to ER stress-inducing reagents (Mimura et al. 2012). IRE1α was also suggested to be oncogenic in glioblastoma through its RNase activity to degrade selective mRNAs by RIDD (Dejeans et al. 2012; Pluquet et al. 2013). However, recent studies suggest a dual role of IRE1α RNase in glioblastoma development, where IRE1α-mediated splicing of XBP1 mRNA is pro-tumorigenic, while IRE1α-mediated RIDD is tumor suppressive (Lhomond et al. 2018).

In contrast, loss of XBP1 promotes tumorigenesis in mouse models of intestinal cancer induced by colitis or by APC mutation (Niederreiter et al. 2013). This appears due to hyperactivation of IRE1α because tumorigenesis actually required IRE1α (Niederreiter et al. 2013). These findings indicate that the IRE1α- XBP1 pathway plays a tumor-suppressor role in cancer in the intestine. Overall, while the under-lying role of IRE1α in cancer initiation is suspected, more recent findings do not fully support a uniform oncogenic role for IRE1α. To conclude, the above observations support the notion that IRE1α-XBP1 plays an oncogenic role in cancer, although the relative contribution of this pathway is highly cell-type-dependent.

8.13 The Role of PERK and ATF4 in Cancer

PERK activation promotes MYC-driven cell transformation and autophagy (Hart et al. 2012), the latter being a well-documented function of ATF4, the downstream signalling effector of PERK-P-eIF2α that initiates cell death. However, there are contradictory findings regarding whether ER stress-induced autophagy promotes tumor progression. While many studies support a cytoprotective role for autophagy in cancer cells (Cubillos-Ruiz et al. 2017; Ma et al. 2014; Ogata et al. 2006), others indicate that autophagy is important for cancer inhibition. For example, Cerezo et al. reported that BiP inhibition by the thiazole benzenesulfonamide HA15 exerts its cancer cell killing effect by causing ER stress to activate autophagy and apoptosis in a manner that requires the apoptosis factor CHOP (Cerezo et al. 2016). Similarly, other independent studies reported that *Chop* gene deletion increases K-Ras*G12V* driven mouse lung cancer (Huber et al. 2013). In addition, *Chop* deletion increases hepatocellular carcinoma in a mouse model of hepatocyte-specific misfolding of urokinase (*MUP-uPA* transgenic mice) (Huber et al. 2013; Nakagawa et al. 2014), which is consistent with CHOP's role in apoptosis induced by ER stress. It is unknown if CHOP plays a tumor-suppressor role in human tumors, although missense mutations in the *Chop* gene were reported in human lung adenocarcinoma (Kan et al. 2010).

8.14 The Role of ATF6 and BiP/ GRP78 in Cancer

Some studies suggest that ATF6α promotes tumorigenesis (Arai et al. 2006), possibly by its downstream effector ER chaperone, BiP. Elevated BiP expression is associated with benefits favoring cancer cell survival (Fu et al. 2007; Pyrko et al. 2007) and can prevent caspase activation (Reddy et al. 2003).

Inhibition of cell division due to G0/G1 cell cycle arrest and entry into quiescence are characteristic of cancer cell dormancy (Aguirre-Ghiso 2007). A main reason for cancer recurrence after radio-and chemotherapies is reactivation of dormant cells (Paez et al. 2012). There also appears to be a link between UPR activation and tumor dormancy as ATF6 is highly expressed in recurrent tumors (Ginos et al. 2004) and correlates with poor prognosis for colorectal cancer (Lin et al. 2007). ATF6 expression is elevated in metastatic lesions compared to the primary tumor (Ramaswamy et al. 2001). These findings suggest that ATF6 may be constitutively active in dormant cells, such as human squamous cell carcinoma (SCC) (Schewe and Aguirre-Ghiso 2008), but studies need to confirm this notion. Knock-down of ATF6 in SCC reduces cancer cell survival and tumor growth via downregulation of adaptive pathways, such as mTOR (Schewe and Aguirre-Ghiso 2008). ATF6 induces expression of proteins associated with tumor transformation (Arai et al. 2006) and chemo-resistance (Higa et al. 2014), which may explain why recurrent tumors are refractory to second rounds of chemotherapy. Finally, forced expression of the activated form of ATF6p50 caused spontaneous colitis and colon cancer in mice (Coleman et al. 2018).

Nevertheless, due to the mutual compensation of the UPR branches, it is challenging to dissect the exact requirement of each UPR sensor in cancer. For example, inactivation of any of the three UPR pathways may result in compensatory activation of alternative UPR pathways. Therefore, caution is necessary to interpret the causal role of individual UPR signalling events that promote or limit tumor initiation and progression.

8.15 The UPR and Immune Surveillance

The ER plays a pivotal role in the synthesis and assembly of the major histocompatibility complex (MHC). After its polypeptide synthesis and ER membrane translocation, the assembly of the heavy and macroglobulin β2m chains of MHC class I (MHC-I) takes place in the ER lumen. The assembly and the subsequent loading of a high-affinity peptide fragment for immune recognition are facilitated by the TAP channel, tapasin, and by the ER chaperones ERp57, calnexin and calreticulin (Blum et al. 2013). Under the stringent ER protein folding quality control, only appropriately folded MHC-I with a peptide cargo is allowed to be exported to the cell surface for antigen display under immune surveillance. Therefore, ER stress is associated with insufficient MHC-I assembly and cell surface presentation (Granados et al. 2009), which is speculated to cause impaired immune surveillance in the tumor microenvironment. Conversely, the ER chaperone GRP94, an HSP90 family member, is well known for its role in facilitating peptide pre- sentation by professional antigen-presenting cells (APCs) (Schild and Rammensee 2000). This peptide presentation function of GRP94 was further mapped to its N-terminal domain compromising the first 355 amino acids (Biswas et al. 2006). It is plausible that ER stress in tumor cells could interfere with the role of GRP94 in facilitating antigen uptake by APCs for its presentation class I and class II MHC molecules, as misfolded protein cargo in the ER lumen can sequester the HSP-like chaperones (Dorner et al. 1988).

8.16 Therapeutic Strategies to Target the UPR

The complexity of ER stress responses has significant potential for therapeutic intervention. The advantage of targeting the UPR is that tumor cells rely more on this pathway for survival than healthy cells, thus providing strategies for selective killing.

8.17 Chemical Chaperones

Broad spectrum chemical chaperones have been identified as low molecular weight compounds that alleviate ER stress by promoting protein folding, preventing protein aggregation and increasing ERAD. The most common ER stress alleviators are 4-phenylbutyric acid (PBA), a short-chain fatty acid also described as a potent histone deacetylase inhibitor, and tauroursode-oxycholic acid (TUDCA), a hydrophilic taurine conjugate of the bile salt ursodeoxycholic acid (Sarvani et al. 2017). It was first proposed that these chaperones may be potent therapeutic agents against metabolic disorders. Treatment with either PBA or TUDCA efficiently resolved hepatic steatosis and enhanced insulin action in the livers of *ob/ob* mice with type 2 diabetes (Özcan et al. 2006). PBA, and especially TUDCA, were also shown to protect against liver injury and regeneration failure as they reduced inflammation, apoptosis and necrosis in both steatotic and non-steatotic livers after partial hepatectomy and ischemia-reperfusion (Ben Mosbah et al. 2010). In HFD-fed mice and in non-alcoholic steatohepatitis (NASH)-prone transgenic mice that express high levels of misfolded urokinase in hepatocytes, treatment with TUDCA or hepatic overexpression of BiP abrogated the signs of NASH: protecting against hepatic steatosis and liver injury characterized by ballooned hepatocytes, increased ROS and cell death (Nakagawa et al. 2014). Similarly, administration of TUDCA to *ob/ob* leptin-deficient obese mice challenged with lipopolysaccharide protected against ER stress-dependent NLRP3 inflammasome activation and liver injury (Lebeaupin et al. 2015). Oral administration of either PBA or TUDCA in ER stress-prone mice with colitis significantly reduced signs of colonic inflammation by alleviating ER stress in colonic epithelial cells (Cao et al. 2013).

TUDCA and PBA are Food and Drug Administration-approved agents as orally active chemical chaperones that reduce ER stress and are being tested in extensive clinical trials. That being said, these chaperones usually require high concentrations due to their poor selectivity, often making them neglected as therapeutic agents. While PBA and TUDCA have proven their safety and potency in reducing ER stress, their direct mechanisms of action have yet to be clearly defined.

8.18 Pharmacological Inhibitors/ Activators

Many pharmacological compounds target distinct UPR signalling molecules (Hetz et al. 2013; Lebeaupin et al. 2018a) (Table 8.1). Nevertheless, many compounds have yet to prove their efficacy and safety *in vivo* to confirm their therapeutic potential.

IRE1α, possessing both a catalytic core in its RNase domain and an ATP-binding pocket in its kinase domain, can be manipulated pharmacologically. The challenge lies in developing selective compounds that interact with one domain without affecting the other. Small molecule inhibitors of the RNase function of IRE1α include 4μ8c (Lebeaupin et al. 2018b;

Tufanli et al. 2017), STF-083010 (Kim et al. 2015; Lebeaupin et al. 2018b; Lerner et al. 2012; Tufanli et al. 2017) and MKC-3946 (Mimura et al. 2012). IRE1α RNase function can also be modulated through its kinase domain by ATP-competitive ligands, forming a new pharmacological class of inhibitors called Kinase-Inhibiting RNase Attenuators (KIRAs) (Ghosh et al. 2014; Han et al. 2009; Morita et al. 2017). Through a conformational change, broad-acting kinase inhibitors APY29 (Kuo et al. 2017; Wang et al. 2012) and clinically-approved sunitinib (gastrointestinal, renal and pancreatic cancer) block IRE1α kinase activity, but allosterically activate IRE1α's RNase domain in yeast (Korennykh et al. 2009). Another compound, selonsertib (GS-4997), showed potential in patients with NASH as a well-tolerated selective inhibitor of ASK1, an important intermediary of IRE1α-JNK1 signal- ling (Loomba et al. 2017), but recently failed a phase 3 clinical trial (Gilead Sciences), further exposing the unmet need for effective liver disease treatments. Selonsertib could nevertheless provide a treatment strategy against multidrug resistance in a variety of cancers (Ji et al. 2019).

Targeting the PERK pathway, the small molecules GSK2606414 (first generation) and GSK2656157 (preclinical development candidate) were developed as pharmacological inhibitors of PERK autophosphorylation (Atkins et al. 2013; Axten et al. 2013), but recent evidence showing off-target effects of these compounds questions their selectivity (Rojas-Rivera et al. 2017). In addition, these compounds destroy pancreatic β-cells, likely because β-cells require PERK-mediated phosphorylation of eIF2α (Mercado et al. 2018). At the expense of pancreatic β-cell survival, GSK2606414 may protect against ER stress-related neurodegenerative decline (Mercado et al. 2018). By preventing eIF2α dephosphorylation through the selective disruption of the PP1-PPP1R15A/GADD34 holoprotein P-eIF2α phosphatase complex, the compounds salubrinal (Vandewynckel et al. 2015), guanabenz (Tsaytler et al. 2011) and its derivative sephin1 (Chen et al. 2019; Das et al. 2015) maintain mRNA translational inhibition. Recent findings challenge the assumption that guanabenz and sephin1 interfere with eIF2α dephosphorylation (Crespillo-Casado et al. 2017), although both drugs do reduce ER stress. A newly discovered and selective phosphatase inhibitor raphin1 targeting PPP1R15B may have potential as an orally available and selective com- pound that improves proteostasis in neurodegen- erative diseases (Krzyzosiak et al. 2018).

While aiming to prevent eIF2α dephosphorylation may exert protective effects against misfolding and a protein overload in the ER in the short-term, persistent inhibition of global translation in cells is poorly tolerated in the long-term. On the contrary, a potent integrated stress response inhibitor (ISRIB, or the more recent 2BAct) was shown to render cells resistant to the effects of eIF2α phosphorylation via eIF2B activation (Sidrauski et al. 2015; Wong et al. 2019), likely a consequence of stabilizing a dimer of the pentameric eIF2B (Tsai et al. 2018; Zyryanova et al. 2018), permitting continued protein synthesis, protecting UPR function and promoting cell survival. In an effort to selectively activate the apoptotic versus the adaptive arm of the UPR, the chemical probe and sulfonamidebenzamide ML291 was developed (Flaherty et al. 2013). ML291 demonstrated efficacy in inducing CHOP-dependent cell death in a number of cell lines, making it a potential candidate for cancer therapy (Flaherty et al. 2014). PDI antagonists, such as PACMAs (Badolato et al. 2017) and bacitracin (Goplen et al. 2006), also represent important approaches for the development of targeted anticancer compounds.

Agents that specifically modulate ATF6 expression or activity are limited and general serine protease inhibitors, such as AEBSF (Okada et al. 2003), are commonly used. A new class of small molecule inhibitors called Ceapins trap full- length ATF6 in ER-resident foci, preventing ER stress-induced trafficking of ATF6 to the Golgi for proteolytic activation (Gallagher et al. 2016). Another strategy involves reprogramming the ER proteostasis environment through the genetic activation of ATF6α by the small molecule N-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (147), shown to attenuate secretion and aggregation of amyloidogenic proteins (Paxman et al. 2018; Plate et al. 2016). Treatment of ischemia/reperfused cardiomyocytes with 147 promoted proteostasis and reduced oxidative stress, while 147 administered *in vivo* improved cardiac performance in mice subjected to acute myocardial infarction (Blackwood et al. 2019).

8.19 Antioxidants

Accumulating evidence suggests that protein folding and production of ROS are closely linked, with persistent ER stress and oxidative stress synergistically initiating apoptotic cascades and playing significant roles in disease pathogenesis (Malhotra and Kaufman 2007). The application of antioxidants not only reduces oxidative stress, but also improves protein folding and secretion to prevent ER stress-induced apoptosis (Han et al. 2015; Malhotra et al. 2008). Accumulation of misfolded clotting FVIII in the ER lumen activates the UPR, causes oxidative stress and induces apoptosis. In mice injected with a vector that encodes aggregation-prone FVIII, feeding with butylated hydroxyl-anisole (BHA), a lipid-soluble antioxidant, reduces levels of UPR activation, oxidative stress and apoptosis and increases FVIII secretion (Malhotra et al. 2008). Mice deficient for *P58IPK*, an ER luminal co-chaperone for BiP, are susceptible to protein-folding defects, reduced pancreatic β-cell mass and function (Han et al. 2015), and multi- systemic neuropathy (Synofzik et al. 2014). In these mice the β-cell failure and diabetes were attenuated when fed with a BHA-supplemented diet (Han et al. 2015). Since efforts to reduce ROS are associated with improved protein folding and cell survival, antioxidant treatment may offer a feasible treatment perspective in protein misfolding diseases and metabolic diseases.

In detoxifying organs such as the liver, the antioxidant response is orchestrated by the highly expressed factor NRF2. NRF2 has been suggested to play a cytoprotective role in response to ER stress-dependent inflammation in animal models with NASH (Okada et al. 2012). Further, pharmacological activators of NRF2 signalling significantly reduced fibrosis in rats with diet-induced NASH, demonstrating a potential strategy to treat NASH patients with hepatic fibrosis (Shimozono et al. 2013). However, NRF2 also induces p62 gene expression through a self-amplifying auto-regulatory loop that creates an oncogenic environment, protecting hepatocellular carcinoma-initiating cells from oxidative stress-induced death (Jain et al. 2010; Umemura et al. 2016). Thus, antioxidants may promote rather than suppress certain cancer development.

8.20 Conclusion

Since tumor cells frequently exhibit a partially active UPR, there is the possibility to preferentially kill these cells by inducing low levels of ER stress, for which normal cells can tolerate and adapt. There are thus multiple ways to modulate ER physiology in an effort to treat diseases related to abnormal ER stress. To confirm their therapeutic potential, the specificity of different pharmacological compounds should be of particular concern, along with the potential side effects due to the artificial manipulation of the signalling pathways of the UPR, which can transition from adaptive to cell death programs. The application of our understanding of the UPR and downstream signalling will prove instrumental in developing novel therapies for a wide range of diseases.

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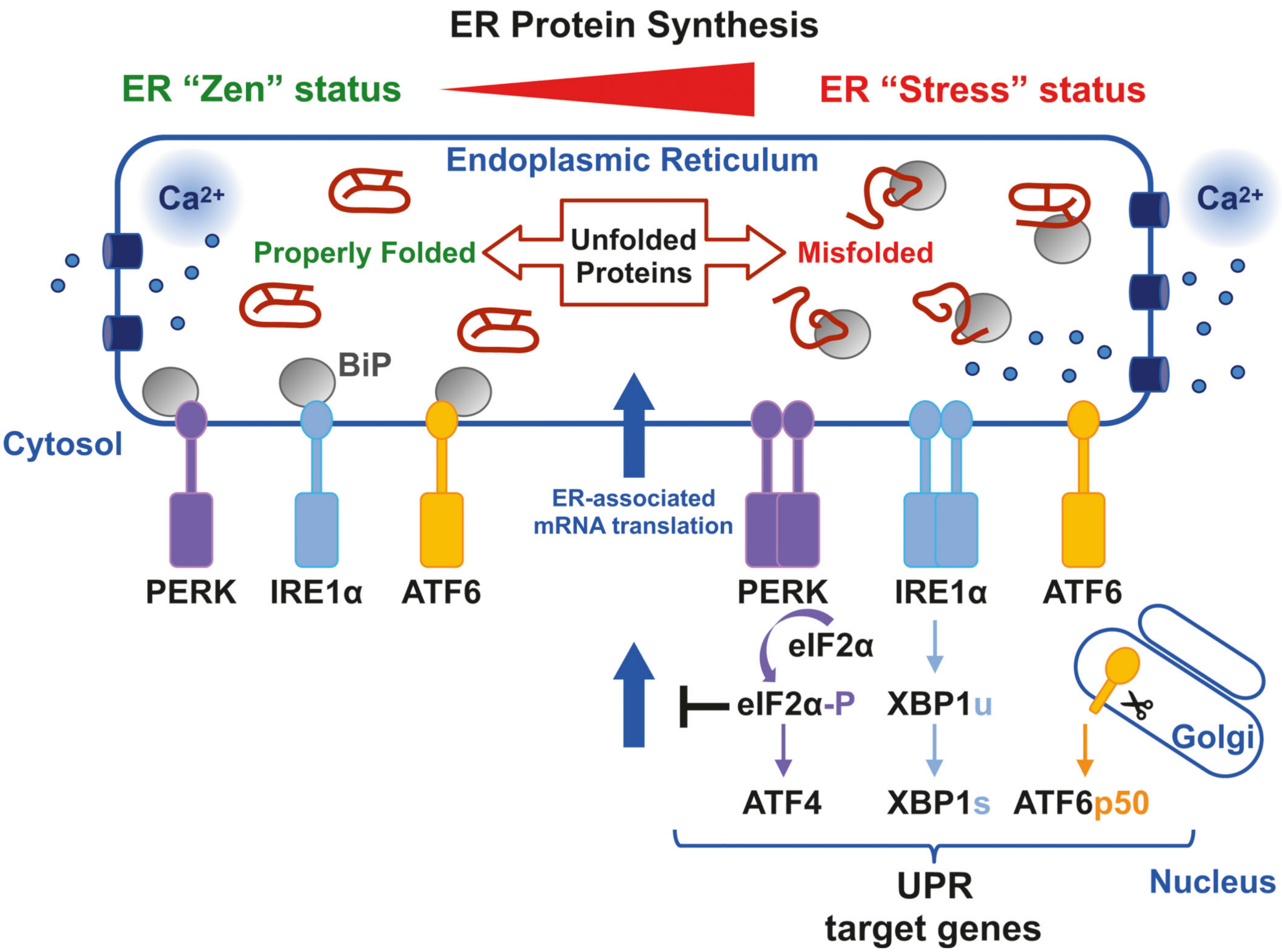

Fig. 8.1.

Schematic model for ER stress and UPR activation

In the ER "Zen" status, the ER maintains protein and Ca^{2+} homeostasis. In the ER "Stress" status, accumulation of misfolded proteins induces the release of BiP from PERK, IRE1α and ATF6. These arms can be subsequently activated in a signaling cascade termed the UPR, which involves the downregulation of translation and the activation of transcription factors that regulate target genes to promote ER homeostasis and cell survival

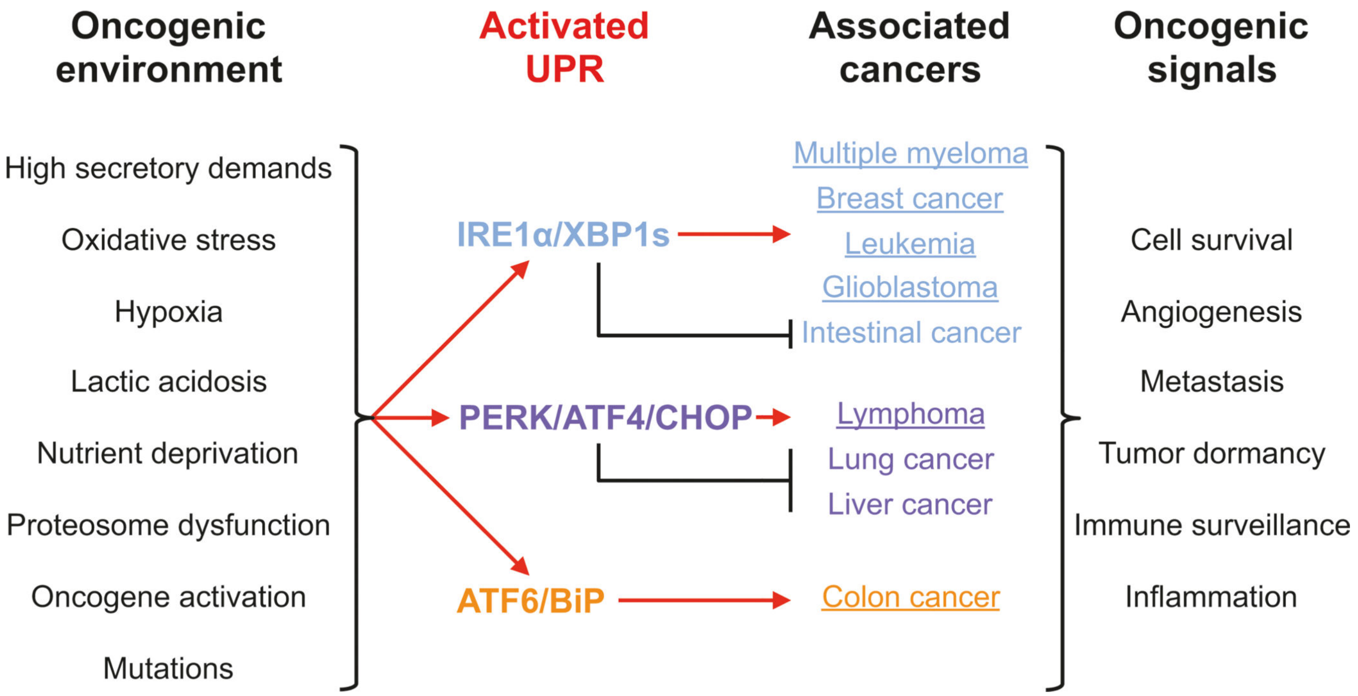

Fig. 8.2.

UPR activation in the oncogenic environment Tumors frequently encounter stressors from the oncogenic environment that compromise protein folding and increase demands on the protein secretory pathway, activating the three branches of the UPR. UPR activation has been reported to promote or prevent cancer development in in a cell-specific manner. The combined outputs of the UPR can send oncogenic signals that influence cancer initiation and progression

Table 8.1

Pharmacological compounds that target UPR pathways with therapeutic implications

Name	Target	Mechanism	Potential therapies	References
4μ8c	IRE1α RNase	Inhibits XBP1 mRNA splicing. Inhibits RIDD function.	Atherosclerosis	Tufanli et al. (2017)
			NAFLD	Lebeaupin et al. (2018a, b)
STF-083010			Diabetes	Lerner et al. (2012)
			Inflammatory diseases	Kim et al. (2015)
			Atherosclerosis	Tufanli et al. (2017)
			NAFLD	Lebeaupin et al. (2018a, b)
MKC-3946			Multiple Myeloma	Mimura et al. (2012)
KIRA6/ KIRA8	IRE1α kinase and RNase	Promotes cell survival under ER stress.	Diabetes	Ghosh et al. (2014)
			Diabetes	Morita et al. (2017)
APY29	IRE1α kinase	ATP-competitive inhibitor that inhibits IRE1α kinase, but increases dimerization/ oligomerization of IRE1α, enhancing RNase activity.	*ND*	Korennykh et al. (2009)
			ND	Wang et al. (2012)
			Kidney cancer	Kuo et al. (2017)
Selonsertib	ASK1	Inhibits ASK1-JNK1 signaling with potential anti-inflammatory, and anti-fibrotic activities.	NAFLD with fibrosis	Loomba et al. (2017)
			Multidrug resistance	Ji et al. (2019)
GSK2606414 GSK2656157	PERK	Inhibits PERK autophosphorylation.	Cancer (tumor development and angiogenesis)	Axten et al. (2013) Atkins et al. (2013)
			Parkinson's disease	Mercado et al. (2018)
Salubrinal	P-eIF2α	Prevents eIF2α dephosphorylation, maintaining mRNA translation inhibition to limit the ER protein load.	Liver cancer	Vandewynckel et al. (2015)
Guanabenz			*ND*	Tsaytler et al. (2011)
Sephin1			Charcot-Marie-Tooth disease and amyotrophic lateral sclerosis	Das et al. (2015)
			ND	Crespillo-Casado et al. (2017)
			Multiple sclerosis	Chen et al. (2019)
Raphin1			Huntington's disease	Krzyzosiak et al. (2018)
ISRIB 2BAct	P-eIF2α	Inhibits P-eIF2α to resume global mRNA translation.	*ND*	Sidrauski et al. (2015)
			ND	Tsai et al. (2018)
			ND	Zyryanova et al. (2018)
			Vanishing white matter disease	Wong et al. (2019)
ML291	CHOP	Selective CHOP inducer with anti-proliferative effects.	*ND*	Flaherty et al. (2013) and Flaherty et al. (2014)
PACMA 31	PDI	PDI inhibitors increases ER stress to reduce cell viability with anti- proliferative effects.	Ovarian cancer	Badolato et al. (2017)
Bacitracin			Glioblastoma	Goplen et al. (2006)
AEBSF	ATF6	Prevents ATF6 proteolytic cleavage in the Golgi and activation.	*ND*	Okada et al. (2003)
Ceapins	ATF6	Traps ATF6 in the ER to prevent activation.	*ND*	Gallagher et al. (2016)

Name	Target	Mechanism	Potential therapies	References
147	ATF6	Localized metabolic activation of ATF6 to enhance proteostasis.	*ND*	Plate et al. (2016)
			ND	Paxman et al.(2018)
			Cardiac ischemia/ reperfusion damage	Blackwood et al.(2019)

ND: therapeutic function in vivo not determined