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REVIEW

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ER stress and/or ER-phagy in drug resistance? Three coincidences are proof

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Abstract

Cancer is influenced by the tumor microenvironment (TME), which includes factors such as pH, hypoxia, immune cells, and blood vessels. These factors affect cancer cell growth and behavior. The tumor microenvironment triggers adaptive responses such as endoplasmic reticulum (ER) stress, unfolded protein response (UPR), and autophagy, posing a challenge to cancer treatment. The UPR aims to restore ER homeostasis by involving key regulators inositol-requiring enzyme-1(IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Additionally, ER-phagy, a selective form of autophagy, eliminates ER components under stress conditions. Understanding the interplay between hypoxia, ER stress, UPR, and autophagy in the tumor microenvironment is crucial for developing effective cancer therapies to overcome drug resistance. Targeting the components of the UPR and modulating ER-phagy could potentially improve the efficacy of existing cancer therapies. Future research should define the conditions under which ER stress responses and ER-phagy act as pro-survival versus pro-death mechanisms and develop precise methods to quantify ER-phagic flux in tumor cells.

Keywords ER Stress, UPR, ER-phagy, Autophagy, Drug resistance

Introduction

Cancers are often surrounded by a unique environment known as the tumor microenvironment (TME), consisting of chemical and cellular components. This environment, characterized by factors such as pH, hypoxia, and cellular elements like immune cells and blood vessels, significantly influences cancer cell growth and behavior [1, 2]. These factors alter cancer cell metabolism and promote therapy resistance by triggering adaptive responses such as endoplasmic reticulum (ER) stress, antioxidant defenses, and autophagy. Consequently, the adaptive responses pose a significant challenge to effective cancer treatment [3, 4].

The endoplasmic reticulum (ER) is a vital organelle responsible for various cellular functions, notably protein synthesis and folding. When the cells experience ER stress caused by factors such as hypoxia, the process of post-translational folding in the ER, which is oxygen-dependent, becomes compromised, accumulating misfolded or unfolded proteins within the ER and disrupting its normal function. This disturbance triggers the unfolded protein response (UPR), a signaling pathway to restore ER homeostasis. The UPR involves three key regulators – inositol-requiring enzyme 1 (IRE1), PKR-like

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ER kinase (PERK), and activating transcription factor 6 (ATF6) – which detect misfolded proteins and coordinate cellular responses to alleviate ER stress [5]. Binding immunoglobulin protein (BiP or GRP78), a chaperone abundant in the ER, plays a crucial role in the UPR by binding to and regulating the activity of IRE1, PERK, and ATF6 [6]. When misfolded proteins accumulate, BiP dissociates from these regulators, allowing them to initiate the UPR cascade and facilitate proper protein folding [7].

Additionally, UPR activation induces autophagy, a cellular process involved in degrading damaged organelles and proteins, thereby maintaining cellular homeostasis and promoting cell survival under stress conditions [8]. Autophagy, although essential for cellular homeostasis, can also promote tumor survival by enabling cancer cells to adapt to stress and evade treatment. Recent research has unveiled the selective nature of autophagy, demonstrating its ability to target specific organelles such as mitochondria, peroxisomes, and the ER for degradation [9].

ER stress and UPR

The endoplasmic reticulum (ER) is an organelle with a large, membrane-like shape. ER structure is classified into two parts: a nuclear envelope domain integrated into rough ER and an ER domain synthesizing ribosomes. The ER interacts with the Golgi, vacuoles, mitochondria, peroxisomes, late endosomes, and lysosomes, which help transfer lipids to the membrane to transmit calcium signals to maintain homeostasis. Other ER functions include phospholipid synthesis, intracellular signaling pathway regulation, and, most notably, the folding of newly synthesized proteins [10]. However, this protein folding function is susceptible to the imbalance between its efficiency and the rate of mRNA translation [11]. In addition, unfolded or misfolded protein accumulates in the ER lumen because of unfavorable conditions such as hypoxia, food deprivation, drug-induced toxicity, acidic extracellular pH, and genetic mutation [12]. These circumstances are toxic for healthy cells, so they act by activating an adaptive pathway called endoplasmic reticulum stress (ER stress), triggering the UPR. UPR aims to reduce protein synthesis and recovery by altering the cascade of ER-associated degradation (ERAD) systems that encode chaperone proteins and the flood of transcription factor-mediated gene expression of the component genes. Therefore, UPR restores intracellular homeostasis and supports mechanical autophagy and cell survival [10].

As mentioned, UPR is activated to protect cells from the aberrant status provoked by misfolded proteins during ER stress. If cells cannot return to their homeostatic status, the UPR system kills them, which means that it probably also suppresses tumors. Nonetheless, multiple pieces of evidence point to the UPR system's function in tumor promotion in cancer cells under ER stress, making the connection between ER stress and UPR in cancer very contentious [13]. Cancerous cells need many nutrients to maintain their highly proliferative condition, frequently engaging in aerobic glycolysis to promote malignant growth and create a particular cancer microenvironment. However, tumor cells can adjust to this challenging microenvironment by inducing ER stress.

Activation of ER Stress and UPR

The inositol-requiring enzyme-1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor-6 (ATF6) pathways are three of the UPR's branching pathways that have been reported to be hyperactivated in many human hematological and solid malignancies [12]. In this review, we will examine the relationship of these pathways with cancer cell growth, invasiveness, immunogenicity, oncogenic driver genes, and drug resistance.

IRE1a-XBP1 pathway

When there is ER stress, IRE1a dissociates from the GRP78/BiP complex and binds to the Hsp47 chaperone at the ER luminal domain [14]. The cytosolic part of IRE1 is then auto-phosphorylated, initiating unconventional splicing of XBP1 mRNA [11, 15]. The spliced form XBP1-S functions as a transcription factor that translocates to the nucleus. There, it interacts with the UPR element and the ER stress-response elements I and II (ERSE-I and ERSE-II) in the promoter region of several genes, triggering the over-expression of several genes [16]. These genes coordinate ER protein folding, secretion, ERAD, lipid production, and ER expansion processes to reduce ER stress [15].

IRE1 activation can lead to the degradation of UPR target mRNAs, including mRNAs that negatively regulate apoptosis, cell proliferation, differentiation, and GRP78/BiP, through a process known as Regulated IRE1-dependent decay (RIDD) [17]. The IRE1a-XBP1s signaling pathway is activated in both tumor and immune cells and is essential for MYC signaling, a well-studied cancer driver gene that directly links UPR and oncogene activation [12]. Analysis of prostate cancer at the transcriptomic level has shown that the activation of the IRE1a-XBP1s pathway is crucial for c-MYC signaling, and inhibiting it can impact tumor progression [18]. However, the expression level of XBP1 can lead to different outcomes; in breast cancer [19], non-small cell lung cancer (NSCLC) [20], and oral squamous cell carcinoma [21], high XBP1 expression is associated with cancer progression. Furthermore, inhibiting IRE1 and reducing XBP1 expression

levels can impede tumor development and angiogenesis in glioma cell lines [13]. Apoptosis is the primary mechanism of cell death, and in the case of the IRE1 pathway, it is promoted when this protein interacts with the tumor necrosis factor receptor-associated factor-2 (TRAF2). This interaction triggers the JUN N-terminal kinase (JNK) pathway, which suppresses BCL-2 activity and activates BIM (also known as BCL2L11), leading to apoptosis [22].

PERK-eIF2α pathway

PERK and IRE1 have homologous luminal domains; therefore, their activation mechanisms are comparable [11]. Indeed, for its activation, PERK must be dimerized and autophosphorylated as a response to ER stress. After, PERK phosphorylates the Eukaryotic initiation factor-2α subunit (eIF2α) [23]. This phosphorylation process and its aftereffects are also known as the integrated stress response (ISR) because other stress-sensing kinases also target eIF-2 [11]. elF2α activation results in both the inhibition of new protein synthesis and the activation of stress-responsive transcription factors such as ATF-4 [24]. PERK pathway activation can be pro-adaptive or pro-apoptotic, depending on its dynamics. When it assumes a pro-adaptative role, ER stress is inhibited through ATF-4, provoking a negative feedback loop by inducing the C/EBP Homologous protein transcription factor (CHOP) expression. CHOP, in turn, activates PPP1R15A (also known as GADD34), which dephosphorylates eIF2 to end the ISR and return translational rates to normal. Otherwise, when ER stress is not reduced, ATF4 has a pro-apoptotic role by upregulating CHOP expression [11, 25].

When adverse environmental conditions affect tumor growth, cancer cells can cause ER stress, disrupting ER homeostasis and activating the PERK-eIF2 branch of the UPR to support adaptation to harsh environmental conditions. For example, PERK activation promotes glioma cell survival under low glucose metabolism stress via AKT activation. As mentioned, the PERK/eIF2 branch is also essential in regulating autophagy to promote cancer cell survival [12]. In a study on lung cancer, Bruceine D (BD) inhibited tumoral cell proliferation via induction of apoptosis and autophagy. In return, when these cells were pre-treated with N-acetylcysteine (NAC), it downregulated PERK levels and inhibited BD-mediated cell death [26]. PERK/eIF2 axis has also been related to tumoral cell growth through other mechanisms. In particular, in pancreatic cancer pre-clinical models, PERK direct inhibition with GSK2656157 could reduce cancer growth [11]. A similar relation between PERK and tumor growth has also been observed in breast cancer progression [27].

PERK is related to cancer cell growth and tumor invasiveness. In a study on breast cancer, it has been reported to promote distant metastasis via regulation of the downstream mediator CREB3L1 [28]. In addition, in pancreatic ductal carcinoma (PDAC), cancer-associated fibroblasts (CAFs) contribute to tumor angiogenesis in vitro and in vivo, undergoing EMT, which is regulated by the PERK-eIF2α-ERK1/2 axis [29]. PERK activation can promote pro-inflammatory cytokines IL-6 and IL-8, which have been shown to protect tumor cells from cell death in renal cell carcinoma by activating downstream survival programs. Even though ER stress-induced inflammation is linked to tumor growth-promoting factors, ER stress may also have an anti-tumor immunity role. ROS-based ER stress, which happens when there is an aberrant increase in ROS-activated UPR, reflected by PERK phosphorylation, can aid in recovering antitumour immunity by triggering the death of immunogenic cells in cancer cells [24, 30].

ATF6a pathway

During ER stress, the ATF6 sensor exits the ER and translocates to the Golgi apparatus. It is cleaved, thereby site 1 protease (S1P) and S2P, releasing a cytosolic fragment with transcription-factor activity. Active ATF6 upregulates GRP78 and GRP94 ER chaperones and induces several genes related to protein folding, lipid biogenesis, and ERAD [11, 31]. Several studies have found high expression levels of ATF6 in various cancer types. This increased level has also been linked to cancer metastasis and recurrence and used as a prognostic cancer marker. For example, ER stress-related ATF6 intervention in CRC has been associated with poor prognosis. Moreover, another study demonstrated that the GREM1 invasion-promoting factor plays its role in this cancer via regulation of ATF6 activation and ATF4 downregulation [12]. In addition, ATF-6 is related to invasion in CRC, and its high expression levels also increase tumor growth [32]. ATF-6 mediated cell proliferation has also been observed in pancreatic cancer patients [33]. Interestingly, ATF-6 expression is also linked to melanocyte neoplastic growth suppression when triggered by RAS oncogenic driver [22].

The relation of ATF6 with tumor immunity has yet to be studied. A study in CRC patients shows that in the absence of inflammation, intestinal dysbiosis, and the innate immune response are stimulated by ATF6 activation in the colonic epithelium, which results in the creation of tumors dependent on the microbiota. Moreover, reduced disease-free survival is linked to abnormal ATF6 expression in CRC patients [32, 34].

A brief description of how different stress conditions such as hypoxia, mutation, nutrient deficiency, and

drugs induce activation of ER-stress and UPR has been reported in Fig. 1.

ER-Phagy

The ER, a hub for many cellular functions, necessitates the maintenance of homeostasis and quality control. In this context, selective ER autophagy emerges as a pivotal mechanism of ER quality control. It operates under normal conditions to maintain the size of the ER and respond to various internal and external cellular stress stimuli. These stress stimuli, such as changes in redox potential, calcium levels, accumulation of misfolded proteins leading to UPR, and exposure to toxins or drugs (such as tunicamycin), are effectively managed by selective ER autophagy. This process, by minimizing ER stress, ensures the continuous function of the ER. [35–38]. Morphometric analyses gave the first report of ER transport for digestion within the lysosomal compartments [39]. Rough ER membranes were initially observed within vesicular structures in the fat bodies of insects during storage granule formation [40]. Additionally, ER fragments were observed in double membrane-bounded autophagic vacuoles (AVs) in the hepatocytes of rats after treatment termination and in pancreatic cells from pigs following subcutaneous cobalt injection [41, 42]. Subsequently, Hamasaki et al. observed the delivery of ER fragments to the vacuoles for degradation during the deficiency of nutrients in yeast [43]. Finally, the Peter Walter research group forged the terminology "ER phagy" (which came from the contractions of "autophagy" and "ER") to explain the selective transport of ER membrane and related fragments after UPR-induced ER membrane expansion in yeast [44, 45].

Types of ER-Phagy

It was observed that Dithiothreitol (DTT) treatment, which induces ER stress and UPR via disulfide bond formation inhibition, led to the formation of autophagosomes containing membrane stacks taken from the UPR-expanded ER. This type of ER turnover, termed micro-ER-phagy, is characterized by the uptake of ER whorls by AVs in a manner that does not depend on canonical autophagic proteins [46]. Therefore, UPR-induced ER turnover is referred to as micro-ER-phagy, which distinguishes it from macro-ER-phagy, triggered by increased expression of vital membrane-bound proteins and nutrient deficiency [47, 48].

Macro-ER-phagy is a type of ER-phagy where autophagosomes fuse with the lysosomes with the help of ER-resident or ER-related receptors [49]. This specific form of ER-phagy gained significant attention after identifying the first ER-phagy receptor in 2015 [50]. Currently, there are eight known membrane-bound mammalian ER-phagy receptors (ERPR), which include members of the family with sequence similarity 134 (FAM134A, FAM134B, FAM134C), translocation protein SEC62

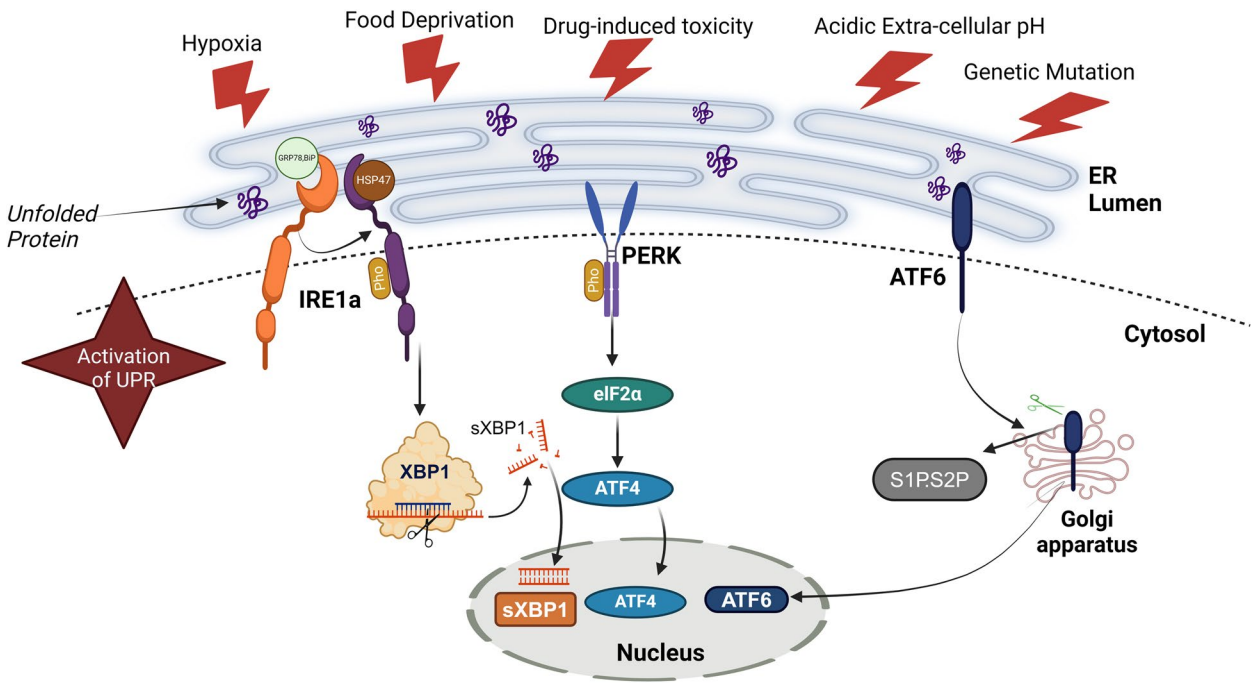

Fig. 1 Activation of ER stress and UPR: Different stress conditions inducing activation of major ER stress and UPR pathways

(SEC62), reticulon 3 (RTN3), atlastin GTPase 3 (ATL3), cell-cycle progression gene 1 (CCPG1), and testis-expressed protein 264 (TEX264) [51–56]. FAM134A/B/C and RTN3L contain a reticulon homology domain (RHD) that allows them to deform ER membranes [57]. Other identified soluble ERPRS include calcium-binding and coiled-coil domain-containing protein 1 (CALCOCO1), CDK5 regulatory subunit-associated protein 3 (C53), and sequestosome 1 (P62) [58–60]. Additionally, other cytosolic autophagy receptors, such as a ubiquitin-binding domain (NBR1) and optineurin (OPTN), can bind to ubiquitinated ER-membrane proteins, indicating their involvement in ER turnover and/or the clearance of polypeptides from the ER membrane [61]. ERPRs have a cytosolic domain comprising LC3 or GABARAP-interacting regions (LIR or GIM), which interact with the autophagic membrane-bound protein LC3/GABARAP, leading to the sequestration of ER membrane or other fragments into autophagosomes for lysosomal/vacuolar clearance [62].

On the other hand, micro-ER-phagy represents a type of ER-phagy that involves the direct transport of cytoplasmic content without the need for ER-phagy receptors (ERPRs) or the formation of autophagosomes. A recent report has highlighted that, during ER stress-mediated ER-phagy, the transport of ER whorls to autophagic vacuoles (AVs) occurs through an endosomal sorting complex essential for transport (ESCRT)-driven micro-ER-phagy [46]. Another ER degradation pathway, ER-to-lysosome-associated degradation (ERLAD), relies on ERPRs but does not involve autophagosome formation [63].

ER-Phagy and cancer

The relationship between ER stress, the UPR, and ER-phagy has been reported [64]. ER stress receptors and ERPRs play a crucial role in maintaining ER homeostasis by detecting and responding to changes within the ER. When activated, ERPRs promote the fragmentation of the ER and transport the fragments for degradation in vacuoles/lysosomes. One significant finding is the distinction between these receptors, with ER stress receptors having large luminal domains that can directly detect changes in ER homeostasis by binding to misfolded proteins or free molecular chaperones [65]. Conversely, ERPRs, except mammalian ERPRs like CCPG1, SEC62, and TEX264, do not have large luminal domains. Therefore, the transduction of anabolic stress signals or the UPRs can occur directly through ER stress receptors due to their exposure to the luminal environment. On the other hand, the transduction of catabolic or "eat-me" signals requires the coordinated action of ERPRs and ER-resident adaptor proteins within the ER. Anabolic UPRs and catabolic ERPRs must be co-regulated to maintain ER size and function according to cellular requirements, such as returning to an average ER size after ER expansion or preventing excessive swelling during ER-stress. ERPR SEC62 is activated during ER stress to help maintain average ER size and function [52]. Furthermore, the activation of FAM134B, CCPG1, and TEX262 during UPR induction increases ER turnover [55, 66].

ER-stress and ER-phagy are crucial parts of all stages of cancer. During the development stage, the rapid proliferation of tumor cells can lead to detrimental events such as starvation and reduced ATP, causing significant damage to the ER and other cellular organelles. When UPR cannot cope with adverse cellular stress, ER-phagy is activated by various signaling pathways. However, if ER-phagy is impaired or stress levels exceed the regulation threshold of ER-phagy, the stimulus can trigger apoptosis-associated proteins, leading to increased cancer cell death [67]. Throughout this process, different signal transduction pathways and related proteins can result in entirely different cellular outcomes. For instance, spliced XBP1s, a transcription factor, can aid angiogenesis; the 78 kDa GRP78/BiP can stimulate tumor cell metastasis and survival via the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway; the PERK/CHOP signaling pathway can promote apoptosis; the deletion of Beclin-1 can lead to the initiation of a tumor; p-eIF2α can weaken tumor invasion; and ATF6 can cause drug resistance [68, 69]. In conclusion, the function of ER in tumorigenesis is highly contextual, with its role possibly varying based on the cancer type, progression stage, and microenvironments.

The relationship between ER-phagy and cancer is complex, as represented in Fig. 2. It is unclear whether ER-phagy helps cancer cells survive and grow or if it leads to death. Understanding the balance between ER-phagy that supports tumor cells and excessive ER-phagy that can cause their death is essential. This corresponds to somewhat similar events that take place as a result of ER-stress in cancer: moderate ER-stress promotes the homeostatic UPR and facilitates cancer survival, whereas unresolved excessive ER-stress can lead to cell death. ER-phagy is triggered through various signal transduction pathways when the UPR is unable to regulate the cellular stress [69]. If the stress intensity is beyond the threshold of ER-phagy, the stress stimuli activate apoptosis proteins to accelerate tumor cell death. A small molecule named Z36 upregulates ER-phagy receptor FAM134B along with other key autophagic proteins like LC3 and ATG9, which ultimately causes excessive ER-phagy flux, causing apoptotic cell death [70]. Studies have revealed that ER-phagy receptors like FAM134B, CCPG1, and TEX264 are pro-tumorigenic in nature, while SEC62 contributes to the recovery process after anticancer therapy, and RTN3L

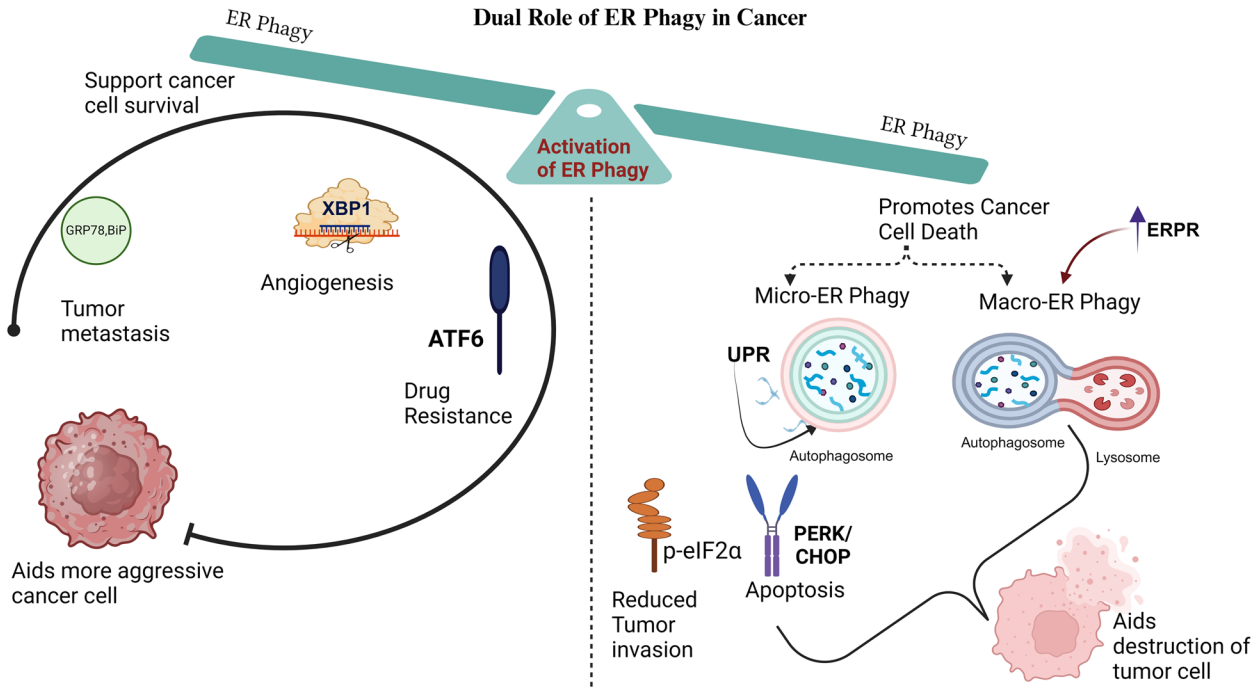

Fig. 2 Dual role of ER-phagy in cancer: Less ER-phagy contributes to cancer cell survival, and more ER-phagy aids cancer cell apoptosis

may degrade the tubular ER [57, 71]. Overexpression of ER-Phagy receptors like SEC62 and associated receptor GRP78 promotes tumor cell proliferation, migration, and invasion [72, 73]. Studies performed by Kasem et al. revealed that FAM134B could inhibit tumor migration and may even prevent tumor metastasis [74].

To summarize, understanding ERPRs could offer insights into combating various cancers, and their role in cancer mitigation needs deep investigation. The challenge lies in quantifying ER-phagy in specific cancer contexts to explore its potential to induce cancer cell death. Utilizing tandem fluorescent protein-tagged ER reporters can be a valuable approach to directly measuring ER-phagy flux in cancer cells [75]. Further, more research is needed to determine if targeting ER-phagy could be an effective anti-cancer strategy in specific cancer contexts (Fig. 3).

ER stress in drug resistance

In the last decades, the fight against cancer has led to the development of new treatment strategies and drugs. Unfortunately, in the majority of cases, cancer develops drug resistance, which leads to the progression of the disease [76]. ER-stress and consequently UPR are processes triggered by many types of treatments [77]. Several studies have demonstrated the key role of GRP78 in drug resistance. Indeed, GRP78 induces drug resistance to endocrine therapy, targeted therapy, and chemotherapy in patients with breast cancer [78–80]. In estrogen-deprivation conditions, GRP78 promotes the survival of estrogen-dependent cells, inhibiting BCL-2-interacting killer (Bik) [81]. Many authors have suggested targeting GRP78 as a novel strategy to reduce drug resistance in the lung, breast, glioblastoma, gastric, head and neck, and colon cancers [82–87].

The three primary regulators of UPR, IRE1, PERK, and ATF6, are also involved in resistance mechanisms. *Zhao* et al. showed that MYC affects the IRE1/XBP1 pathway in breast cancer, and pharmacological inhibition of IRE1 increases the efficacy of docetaxel chemotherapy in vivo [88]. In KRAS mutant colorectal cancer cell lines, IRE1 knockout sensitizes to MEK inhibitor treatment [89]. In acute myeloid leukemia, IRE1 inhibition synergizes with bortezomib and AS2O3; the authors demonstrated how IRE1 activates the pro-survival pathway [90]. The IRE1α endoribonuclease domain inhibitor MKC-3946 blocks the alternative splicing of XBP, increasing the effect of bortezomib and 17-AGG in multiple myeloma (MM) cells [91]. A mesenchymal subpopulation in pancreatic cancer shows increased sensitivity to inhibition of the IRE1-MKK4 arm of the UPR, suggesting this role in conferring tumorgenicity and drug resistance to these cells [92]. Targeting this UPR regulator with its inhibitor (4μ8C) in colon cancer cells overcomes 5-FU resistance by ABC transporter's downregulation [93].

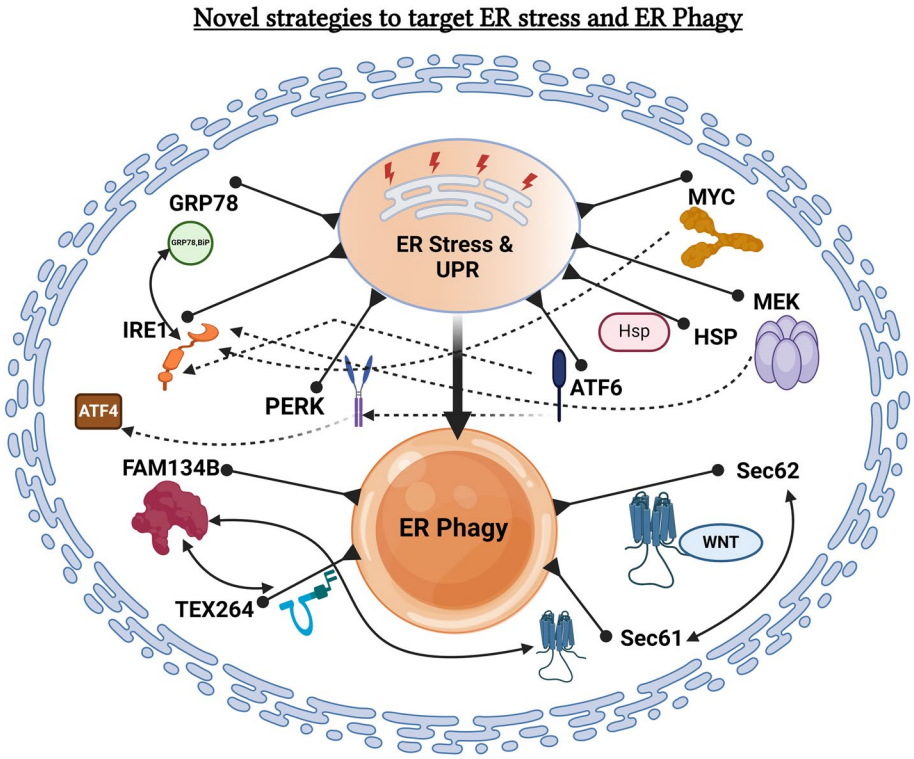

Fig. 3 Novel strategies to target various signaling pathways and molecules that play a crucial role in modulating ER-stress and ER-Phagy

Salaroglio et al. demonstrated that the PERK/NRF2/MRP1 axis drives Multi-Drug Resistance (MDR) in colorectal cancer cells, and PERK silencing sensitizes cells to oxaliplatin, 5-FU, and doxorubicin treatments [94]. PERK/NRF2 interaction also protects acute myeloid leukemia cells from ROS-induced apoptosis, affecting autophagy [95]. Other authors showed how this axis is fundamental for drug resistance in the breast [96]. PERK inhibition also increases the effectiveness of BRAF inhibitors in melanoma cells; this effect is due to the ER stress-induced autophagy blockade and affects the PERK-eIF2α-ATF4 axis [97]. PERK has also been correlated to the immune microenvironment. On the one hand, in murine breast cancer cell lines, the inhibition of PERK suppressed the immunogenic cell death (ICD) triggered by the chemotherapy with Oleadrin. This means that anti-tumor immune surveillance, which can be increased by ICD activation, was decreased [98]. The multikinase inhibitor Sorafenib (standard treatment for advanced hepatocellular carcinoma) resistance is overcome in vitro on HCC cells by inhibiting the PERK/ATF4 axis, suggesting it is a possible target for sorafenib drug resistance cases [99]. ATF4 overexpression mediates cisplatin and 5-FU resistance in esophageal squamous cell carcinoma cells through up-regulation of STAT3 [100], while in gastric cancer, it promotes chemoresistance, affecting SIRT1 [101]. PERK inhibition also promotes sensitization of basal breast cancer cells to doxorubicin treatment [102].

The other UPR regulator, ATF6, drives the imatinib (TKi) resistance in K562R (leukemia) cells, and its activation is due to protein disulfide isomerase A5 (PDIA5) [103]. In gastric cancer, ATF6 drives 5-FU resistance; it is regulated by JAK2/STAT3 pathway [104]. ATF6 silencing sensitizes squamous carcinoma cells to doxorubicin treatment, affecting the activation of the Rheb-mTOR pathway [105]. *Meng* et al. discovered that inhibitors of DNA1 (ID1) and ATF6 high expression in ovarian cancer patients correlated with resistance to cisplatin and paclitaxel, showing that this effect was due to STAT3/ATF6-induced autophagy [106]. Bortezomib and carfilzomib-resistant myeloma cells have upregulated all three pathways of UPR (IRE1-PERK-ATF6), both baseline and after treatment with these inhibitors [107]. In non-small cell lung cancer (NSCLC) cells, patient-derived ATF6 is upregulated after chemotherapy, and it is fundamental for the recruitment of cancer-associated fibroblasts (CAF), which create a pro-inflammatory microenvironment that favors drug resistance [108]. HSP27 is a heat shock protein linked to ER stress [109]. It is involved in resistance to several types of drugs, such as doxorubicin, trastuzumab, and gemcitabine [110–112].

ER-phagy in drug resistance

FAM134B

The role of ER-phagy in anti-cancer drug resistance showed very poor evidence. According to the PubMed database, inputting with the MeSH syntax (ER-phagy) and (drug resistance) only outputted seven results from 2010 up to now, of which only three are in the field of cancer. Indeed, fascinating research about the anti-cancer effect of Brigatinib, an Anaplastic Lymphoma Kinase (ALK) inhibitor approved for the treatment of ALK-positive non-small-cell lung cancer (NSCLC) and Colorectal Cancer (CRC), was discovered. Notably, in ALK-negative patients affected by CRC, Brigatinib promotes ER stress due to the accumulation of the oxysterol-binding protein-related protein 8 (ORP8) in its de-ubiquitinated form, with the relative inhibition of cell growth and the activation of the apoptotic machinery. In response to this insult, the CRC cells activate a cytoprotective FAM134B-mediated ER-phagy, which reduces the sensitivity of the cancer cells to the drug [113]. Conversely, in hepatocyte carcinoma (HCC), the FAM134B silencing enhances the efficacy of the treatment with Sorafenib. This is a small molecule, typically used for the treatment of some cancers because of its Raf/Mek/Erk Kinases inhibition activity, which can also promote cytotoxicity in HCC by reducing the biosynthesis of glutathione with the relative activation of the ferroptosis machinery. However, ER-phagy seems to cross-talk differently with ferroptosis, suggesting a more complex interaction compared to others with metabolite-specific autophagic degradation processes [114]. Later, with renewed additional MeSH syntax (ER stress), the database produced more than 900 results. Among these studies, the authors mainly highlighted the role of many proteins involved in the ER-stress pathways, but are contemporarily able to affect the sensitivity of the cells to different anti-cancer drugs. Interestingly, most of these proteins interact with the ER-phagy regulator FAM134B.

Sec61

Several authors demonstrated that the Sec61 channel and its components play a crucial role in tumor initiation and progression. In particular, elevated expression of Sec62 has been reported at different stages of some cancers, even if its role in the development of the disease remains elusive. In CRC, the overexpression of Sec62 correlates with poor patient survival due to a more stem-like phenotype switch of the CRC cells and enhanced drug resistance [115]. From a molecular point of view, Sec62 activates the Wnt/β-catenin pathway by blocking the β-catenin destruction complex scaffolding. In this condition, β-catenin can migrate into the nucleus, recognize its consensus TCF/LEF sequences, and transactivate the expression of some genes involved in drug resistance [116]. The Sec62 protein is frequently upregulated in Head and Neck Squamous Cell Carcinoma (HNSCC) patients [117]. Recent studies correlated the Sec62 overexpressing HNSCC with less sensitivity to the Thapsigargin-analogue named Mipsagargin, an irreversible inhibitor of the Sarco-/Endoplasmic Reticulum Calcium ATPase (SERCA) [118]. This drug can prevent the reuptake of calcium ions from the cytosol to the ER, showing an antiproliferative activity in prostate cancer [119]. In particular, the activity of the Sec61 complex is modulated by its regulatory subunit Sec62, which directly interplays with Calmodulin on the cytosolic surface and with BiP on the ER luminal surface [120–122]. This mechanism is unbalanced in Sec62 over-expressing HNSCC patients, where the calcium homeostasis is impaired and the cancer cells resist Mipsagargin. In this context, the Calmodulin antagonist Trifluoperazine, currently adopted for treating schizophrenia, can re-sensitize the tumor cells to the Mipsagargin by directly modulating the activity of the gatekeeper Sec62. This mechanism promotes the increase of cytosolic calcium levels and the relative activation of the apoptotic machinery [117]. The oncogenic role of the Sec61 complex has also been highlighted in Multiple Myeloma (MM). Recent studies on in vitro and in vivo pre-clinical models demonstrated that the selective inhibition of Sec61 with the lipid diffusible bacterial toxin mycolactone re-sensitizes the MM cells to the proteasome inhibitor Bortezomib (Bzb) or the immunemodulator Lenalidomide (Len). In particular, the authors found that mycolactone induces additional proteotoxic stress in the MM cells, which activates a pro-apoptotic ER-stress-mediated response, overriding the MM cells' acquired resistance to Bzb and Len [117, 123].

The Sec61 channel is not the only FAM134B interactome protein involved in anti-cancer drug resistance. The Serine/threonine-protein kinase WNK1, involved in the regulation of the cell sodium and chloride ions level by modulating the activity of several Epithelial Sodium Channel (ENaC), plays a crucial role in the resistance to the ALK and Proto-Oncogene C-Ros-1 (ROS1) inhibitor Crizotinib, in NSCLC patients. Usually, the ROS1 gene rearrangement occurs in NSCLC patients without other oncogenic drivers [124]. These patients are initially sensible to crizotinib until they accumulate some other critical mutations in the ROS1 gene, developing some drug resistance mechanisms. Nevertheless, a case report based on a patient with the described clinical conditions demonstrated that developing a ROS1-WNK1 fusion protein can revert the tumor phenotype, re-sensitizing the patient to Crizotinib [125].

TEX264

The Testis-expressed protein 264 (TEX264) is a receptor involved in the ER-phagy, which directly interacts with LC-3 and GABARAP family proteins and indirectly with the receptor FAM134B [126]. The TEX264 protein is vital in the Osteosarcoma resistance to the Camptothecin class of compounds (CPT). The CPT is an inhibitor of the Eukaryotic topoisomerase 1 (TOP1), an enzyme that ensures DNA replication and transcription efficacy. In some cancers, TOP1 represents one of the significant drivers of genome instability because of the stabilization of the TOP1 cleavage complex (TOP1cc), a molecular intermediate generated by the covalent binding of TOP1 with DNA adducts [127]. The TEX264 mediates the resistance to CPT, promoting the degradation of the DNA adducts and reducing the relative cancer cell cytotoxicity. This receptor is associated with DNA replication forks at the nuclear periphery, where it bridges the interaction between the TOP1ccs and the ubiquitin-directed protein unfoldase p97 complexed with the SPRN metalloprotease [128].

The ER tubule turnover is also regulated by many proteins typically involved in the canonical autophagy machinery scaffolding, such as the Autophagy protein 8 (Atg8) family members, namely LC3 and GABARAP. The ER-phage selective regulator FAM134B directly binds LC3 and GABARAP through some domains at its C-terminal to promote the autophagosome vesicle scaffolding [129]. Interestingly, the FAM134B receptor shows a more potent and selective ability in binding the GABARAP receptor, compared to LC3, enhancing the activation of the ER-phagy [130].

While ER-phagy is critically important in the context of cancer drug resistance, our search reveals a notable gap: there are currently no definitive inhibitors designed to target this process. This lack of targeted solutions highlights an urgent area for further investigation and innovation. To date, no clinical trials have been established that focus directly on ER-phagy, and current strategies involving the modulation of FAM134B, RTN3, and SEC62 have yet to transition into practical clinical applications. However, it is worth noting that a limited number of clinical and preclinical studies have sought to indirectly address ER-phagy by modulating the associated receptors linked to ER stress and ER-phagy, as detailed in the list below. This burgeoning field presents a significant opportunity for future advancements and breakthroughs that could enhance therapeutic strategies against cancer (Table 1).

Conclusion

This comprehensive review underscores the intricate interplay between ER stress, the UPR, and ER-phagy within the tumor microenvironment, highlighting their significant roles in cancer progression and drug resistance. ER stress and the UPR pathways, particularly the IRE1, PERK, and ATF6 arms, are pivotal in adapting cancer cells to stressful conditions, promoting survival, and contributing to the complexity of drug resistance mechanisms. These pathways orchestrate a wide range of cellular responses, from modifying protein folding capacities to initiating autophagy, thereby influencing cancer cell fate under therapeutic stress.

ER-phagy emerges as a crucial mechanism for maintaining ER homeostasis, selectively degrading portions of the ER to manage misfolded protein loads and other stress-related damages. The discovery and characterization of ER-phagy receptors have provided new insights into how cells regulate the quality and size of the ER, which is vital for cell survival under stress. However, the dual role of ER-phagy in cancer—supporting survival or triggering cell death—presents a nuanced therapeutic target. Understanding this balance is crucial for

Table 1 List of studies indirectly targeting ER-Phagy and associated receptors

ER-Phagy/ associated receptors	Inhibitors	Disease condition	Reference studies/ Clinical trials
IRE1 inhibitor	MKC8866	Glioblastoma	[131]
PERK inhibitor	AMG44	Cancer	[132]
PERK inhibitor	GSK2656157	Pancreatic Cancer	[11]
ER stress inhibitors (GRP78, PERK, IRE1α, XBP-1, UPR)	Metformin	Endometrial Cancer, Polycystic Ovary Syndrome	[133], NCT02302326
ER stress inhibitors	4-Phenylbutyric acid (4-PBA)	Hepatocellular carcinoma	[134]
ER stress inhibitors	Tauroursodeoxycholic acid (TUDCA)	Hepatocellular carcinoma	[135]
FAM134	SGC-CK2-1	Osteosarcoma	[136]
FAM134B	Vitexin	Glioblastoma, Melanoma	[137]
FAM134B	Z36	Cervical Cancer	[70]

developing strategies that might manipulate ER-phagy for cancer therapy.

The association of ER stress responses with drug resistance offers a promising avenue for therapeutic intervention. Targeting the components of the UPR, such as GRP78 and the primary regulators (IRE1, PERK, ATF6), could potentially overcome resistance and improve the efficacy of existing cancer therapies. Furthermore, the modulation of ER-phagy, either to promote cancer cell death or to prevent excessive survival support, remains an area ripe for exploration.

Future research should focus on defining the conditions under which ER-stress responses and ER-phagy act as pro-survival versus pro-death mechanisms. Additionally, developing precise methods to quantify ER-phagic flux in tumor cells will be crucial. By deepening our understanding of these processes, we can unveil novel therapeutic targets and strategies, potentially leading to more effective treatments for cancer patients, particularly those who have developed resistance to conventional therapies.

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Authors' contributions
S.K.P., V.D.V., L.M.: Conceptualization, Writing- original draft preparation, Review and Editing, Figure Preparation A.R., I.R.S., S.C.: Writing- original draft preparation N.R., V.D.: Conceptualization, Writing- original draft preparation, Review and Editing, Supervision.

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