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REVIEW ARTICLE OPEN

Endoplasmic reticulum stress—a key guardian in cancer

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Endoplasmic reticulum stress (ERS) is a cellular stress response characterized by excessive contraction of the endoplasmic reticulum (ER). It is a pathological hallmark of many diseases, such as diabetes, obesity, and neurodegenerative diseases. In the unique growth characteristic and varied microenvironment of cancer, high levels of stress are necessary to maintain the rapid proliferation and metastasis of tumor cells. This process is closely related to ERS, which enhances the ability of tumor cells to adapt to unfavorable environments and promotes the malignant progression of cancer. In this paper, we review the roles and mechanisms of ERS in tumor cell proliferation, apoptosis, metastasis, angiogenesis, drug resistance, cellular metabolism, and immune response. We found that ERS can modulate tumor progression via the unfolded protein response (UPR) signaling of IRE1, PERK, and ATF6. Targeting the ERS may be a new strategy to attenuate the protective effects of ERS on cancer. This manuscript explores the potential of ERS-targeted therapies, detailing the mechanisms through which ERS influences cancer progression and highlighting experimental and clinical evidence supporting these strategies. Through this review, we aim to deepen our understanding of the role of ER stress in cancer development and provide new insights for cancer therapy.

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FACTS

- Endoplasmic reticulum stress (ERS) plays an important role in tumor development.
- The unfolded protein response (UPR) is the main response of the endoplasmic reticulum (ER) to external stimuli.
- Targeting endoplasmic reticulum stress (ERS) may be a potential strategy for cancer therapy in the future.

OPEN QUESTIONS

- What are the pathways by which endoplasmic reticulum stress (ERS) acts in different cancers?
- How does endoplasmic reticulum stress (ERS) affect the tumor microenvironment?
- How to improve the effectiveness of cancer treatment by combining anti-ERS with anti-tumor drugs?

INTRODUCTION

The endoplasmic reticulum (ER) is the central biosynthetic hub of the cell. It orchestrates the synthesis of proteins (secretory and transmembrane proteins, along with certain cytoplasmic proteins) and lipids [1, 2]. According to the presence or absence of ribosomes on the surface, ER is dichotomized into the smooth ER (without ribosomes) and rough ER. The smooth ER prioritizes lipidogenesis, while the rough ER primarily facilitates protein synthesis and maturation, thereby functioning as a key manufacturing site for a variety of membrane-bound and secretory proteins. Additionally, the ER is essential not only for the synthesis and processing of these proteins but also for the synthesis and modification of proteins destined for other organelles, such as lysosomal proteins. In normative physiological paradigms, the ER quality control system stringently supervises the biogenesis and maturation of proteins to ensure proper conformational folding [3]. When proteins are not folded correctly, molecular chaperones identify these abnormalities and move them into the cytoplasm through a pathway opened by Hrd1-mediated autoubiquitination [4], subsequently subjecting them to the rigors of the endoplasmic reticulum-associated protein degradation pathway (ERAD) for degradation by the 26s proteasome [5]. Conversely, when exposed to pathological stimuli such as glycosylation inhibition, disruptions in ER Ca^{2+} homeostasis, disulfide bond disruption, intracellular hypoxia, pH fluctuations, and the accumulation of damaged DNA [6, 7], the ER's homeostatic equilibrium is disturbed. This leads to a cascade of stress responses that ensure cellular viability in adverse conditions, exemplifying the cellular adaptive mechanisms to internal environmental changes, called endoplasmic reticulum stress (ERS).

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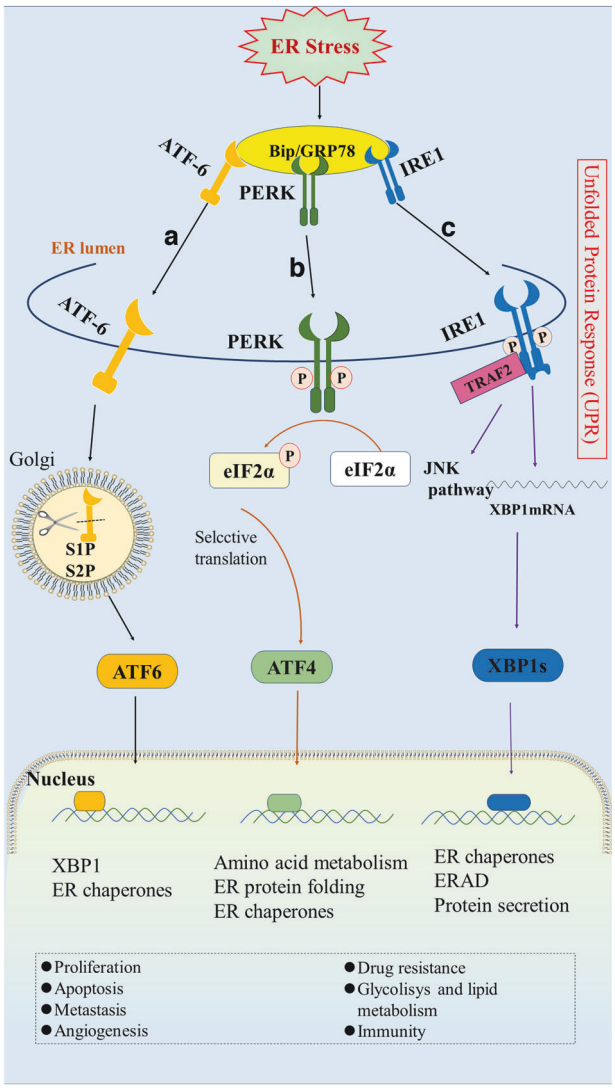

Fig. 1 Schematic representation of the unfolded protein response in tumors. In the endoplasmic reticulum, the ERS-induced unfolded protein response (UPR) promotes tumor progression via three pathways: **a** The activating transcription factor 6 (ATF6) undergoes sequential proteolytic cleavage by site-1 and site-2 proteases (S1P and S2P), facilitating the generation of its active form. This form then translocates to the nucleus and activates numerous downstream targets. **b** Upon ERS, PKR-like ER kinase (PERK) is released from Bip/GRP78 and undergoes self-oligomerization and phosphorylation. Consequently, it phosphorylates eIF2α and activates ATF4. **c** IRE1 is released from Bip/GRP78, then undergoes dimerization and autophosphorylation, subsequently catalyzing the splicing of XBP RNA and regulating a cascade of downstream reactions.

ERS is the response of the ER to external stimuli, which may encompass the ER overload response, sterol regulatory cascade response (SRECR), and unfolded protein response (UPR) [8]. The UPR is a compensatory system triggered by disruptions caused by unfolded proteins within the ER, representing the most frequently encountered and crucial type of ERS. It entails a highly intricate mechanism, incorporating a complex network of intracellular signaling pathways. This system not only regulates the removal of misfolded proteins but is also coupled with an increase in ER size and folding capacity, thereby maintaining the homeostatic balance of the ER. The UPR process involves three ER transmembrane proteins: inositol-requiring enzyme 1 (IRE1), PKR-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6), which function as molecular sensors that instigate the process by activating the downstream pathway; notably the Bip/GRP78 signaling cascade [9]. In the absence of unfolded proteins, these transmembrane units engage dynamically with the regulatory chaperone Bip/GRP78 within the ER. However, the accumulation of unfolded proteins induces a conformational transition in Bip, modulating its affinity for these transmembrane proteins and precipitating its release. Notably, IRE1 distinguishes itself as a principal transmembrane protein possessing dual enzymatic functionalities—kinase and ribonuclease. These are enveloped within an N-terminal luminal sensing domain and a C-terminal cytosolic effector domain [10]. Under physiological conditions, the luminal domain of IRE1α interacts with the Bip/GRP78 regulatory protein. With the onset of ERS, Bip plays a central role as a sensor, detecting subtle stress variations within the ER while simultaneously acting as an Hsp70 chaperone in its binding to IRE1α. During such stress-induced states, Bip employs its substrate-binding domain to recognize misfolded proteins, thereby triggering a decrease in the affinity of its nucleotide-binding domain for IRE1α. This sequence of molecular events culminates in the ATP-driven dissociation of IRE1α from Bip. The liberated IRE1α monomer undergoes dimerization and autophosphorylation, activating its ribonuclease function, which catalyzes the splicing of XBP1 mRNA at the proximal end of the ER membrane and encourages its transcription and translation, thus regulating a cascade of downstream reactions [11]. Analogous to IRE1, the activation of PERK is instigated by the heightened affinity of Bip/GRP78 for unfolded proteins. This facilitates the release of PERK's luminal domain from Bip, allowing oligomerization and autophosphorylation processes to occur in PERK monomers. Upon activation, PERK phosphorylates eukaryotic initiation factor 2 (eIF2α), thereby driving the translation of downstream open reading frames—such as transcription factor ATF4—and influencing key biological procedures including amino acid biosynthesis and glycolysis [12]. ATF6 was initially recognized as an associating protein of serum response factors, existing as a type II transmembrane protein anchored to the ER [13]. This protein is characterized by its transient activity and a notably brief half-life of just 2 h, ranking it amongst the cohort of short-lived proteins [14]. In contrast to PERK and IRE1, ATF6 activation occurs within the Golgi apparatus. Here, resident ATF6 undergoes proteolytic cleavage by S1P and S2P proteases, giving rise to an active ATF6 variant that regulates several downstream elements including Bip/GRP78, GRP94, ERAD components, XBP1, the 58 kDa protein (P58IPK/DNAJC3), and CHOP, thereby playing a pivotal role in directing the UPR [15–18]. Moreover, ATF6 participates in heterodimerization with XBP1, a downstream effector of IRE1, enhancing ERAD. Importantly, this heterodimer exhibits increased affinity for UPR compared to its XBP1 homodimer counterpart under similar conditions [16] (Fig. 1).

ERS has been implicated as a central factor in diverse pathologies, including type II diabetes, toxoplasma infection, and ischemia/reperfusion injury [19–21]. A convergence of modern research findings underscores the crucial role of ERS within the oncogenic narrative, shaping cancer progression from inception through to advancement. This review examines the role and molecular foundations of ERS in cancer, delving specifically into its influence on various biological processes such as proliferation, apoptosis, metastasis, angiogenesis, drug resistance, cellular metabolism, and immune response (Fig. 2). The ensuing discourse will offer insights into the complexities of ERS in tumorigenesis and cancer evolution, providing a strategic blueprint for the design of cancer therapeutics.

THE ROLE OF ERS IN CANCER

The advancement of neoplasms is invariably influenced by a spectrum of factors intrinsic to the tumor microenvironment

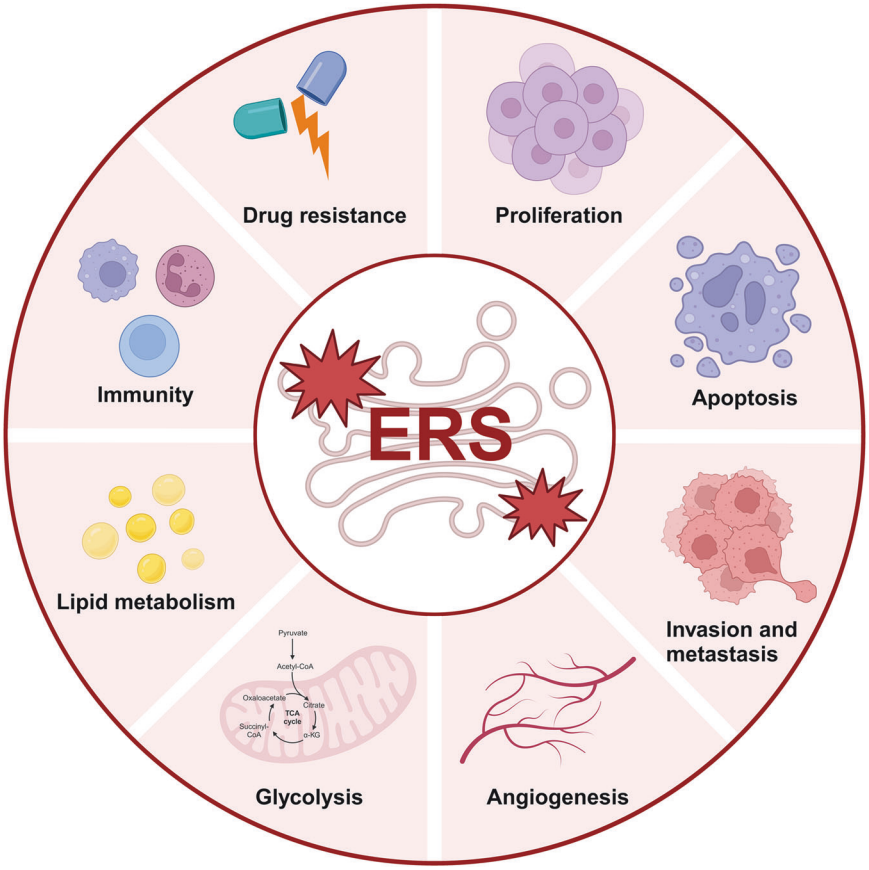

Fig. 2 The roles of ERS in tumor progression. The endoplasmic reticulum (ER) serves several crucial functions in tumors, including the promotion or inhibition of tumor proliferation, induction of cell apoptosis, enhancement of tumor invasion and metastasis, stimulation of tumor angiogenesis, facilitation of tumor cell glycolysis and lipid metabolism, support of tumor immune evasion, and mediation of drug resistance.

(TME), including hypoxia, pH fluctuations, reactive oxygen species (ROS), and a variety of cellular metabolites. In this milieu, the ER orchestrates a complex response to external stimuli, facilitating the ongoing growth of tumors. This discussion seeks to elucidate the pivotal role and intricate molecular mechanisms of the UPR within oncogenic paradigms. It will explore its ramifications on tumor proliferation, apoptosis, metastasis, angiogenesis, drug resistance, cellular metabolism, immune response, and the resilience of neoplasms to pharmacological interventions.

Proliferation

The unrestrained division and rapid proliferation of cancerous cells are essential for their accelerated growth. Within this dynamic, tumor cells are constantly influenced by a number of intracellular and extracellular stimuli, ERS plays a mitigating role in facilitating tumor cell proliferation [22] (Fig. 3). In hepatocellular carcinoma (HCC), TRIM25 has been found to target and degrade Keap1, consequently activating Nrf2 and fostering HCC cell proliferation by modulating the UPR signaling pathway and ERAD. Specifically, TRIM25 mediates its effects via the IRE1–JNK branch of the UPR pathway under conditions of ERS, functioning as a downstream effector [23]. In melanoma, UPR activation catalyzes tumor cell proliferation via the IL-6/STAT3 axis [24]. In non-small cell lung cancer (NSCLC), elevated expression of PRL11 promotes tumor cells proliferation through UPR and autophagy [25]. In addition, IRE1–XBP1 axis, the downstream of the UPR pathway could significantly accentuate MYC-driven tumorigenic progression in breast cancer and urothelial carcinomas [26]. Similarly, extracellular vesicles from cancer cells exploit the UPR's IRE1α pathway to instigate oncogenic transformation in bladder cancer [27]. The pro-tumorigenic influence of IRE1α is proposed to be related to its phosphatase function, wherein in reaction to ERS stimuli, IRE1α recruits TRAF2 through its phosphatase domain, eventually prompting the activation of c-Jun N-terminal kinase (JNK) and nuclear factor κB (NF-κB) pathways and thereby bolstering oncogenesis [28, 29]. Conversely, in the context of ERS signaling, the PERK pathway exerts a tumor-suppressive effect, particularly in breast cancer, where PERK activation significantly inhibits tumor proliferation. However, the molecular intricacies of this phenomenon remain to be elucidated [30].

ATF6 is emerging as a key downstream effector in the field of ERS. It has a spectrum of roles in oncological biology. It has been elucidated that elevated ATF6α is closely associated with the progression of prostate cancer. Furthermore, it could regulate arachidonic acid metabolism via the ATF6α–PLA2G4A signaling pathway to promote prostate cancer progression [31], or promote the malignancy through a reciprocal negative feedback mechanism with PTEN [32]. In addition, ATF6 plays a pivotal role in maintaining BRCA-1 expression. This enables colon cancer cells to evade DNA damage and enhance their viability [33]. In colorectal cancer, phosphorylated ATF6 has been demonstrated to promote tumor development by inducing gut microbiome dysbiosis and activating the TIR domain-containing adapter-inducing interferon-β (TRIF)/STAT3 signaling cascade [34]. Moreover, ATF6 has been demonstrated to accelerate the proliferation of cervical cancer cells via the MAPK pathway [35]. However, ATF6 exhibits a tumor suppressor effect when combined treatment with clofoctol and sorafenib in prostate cancer [36].

In certain circumstances, the inhibition of ERS can facilitate tumor survival. For example, in BRAF-mutant uveal melanoma,

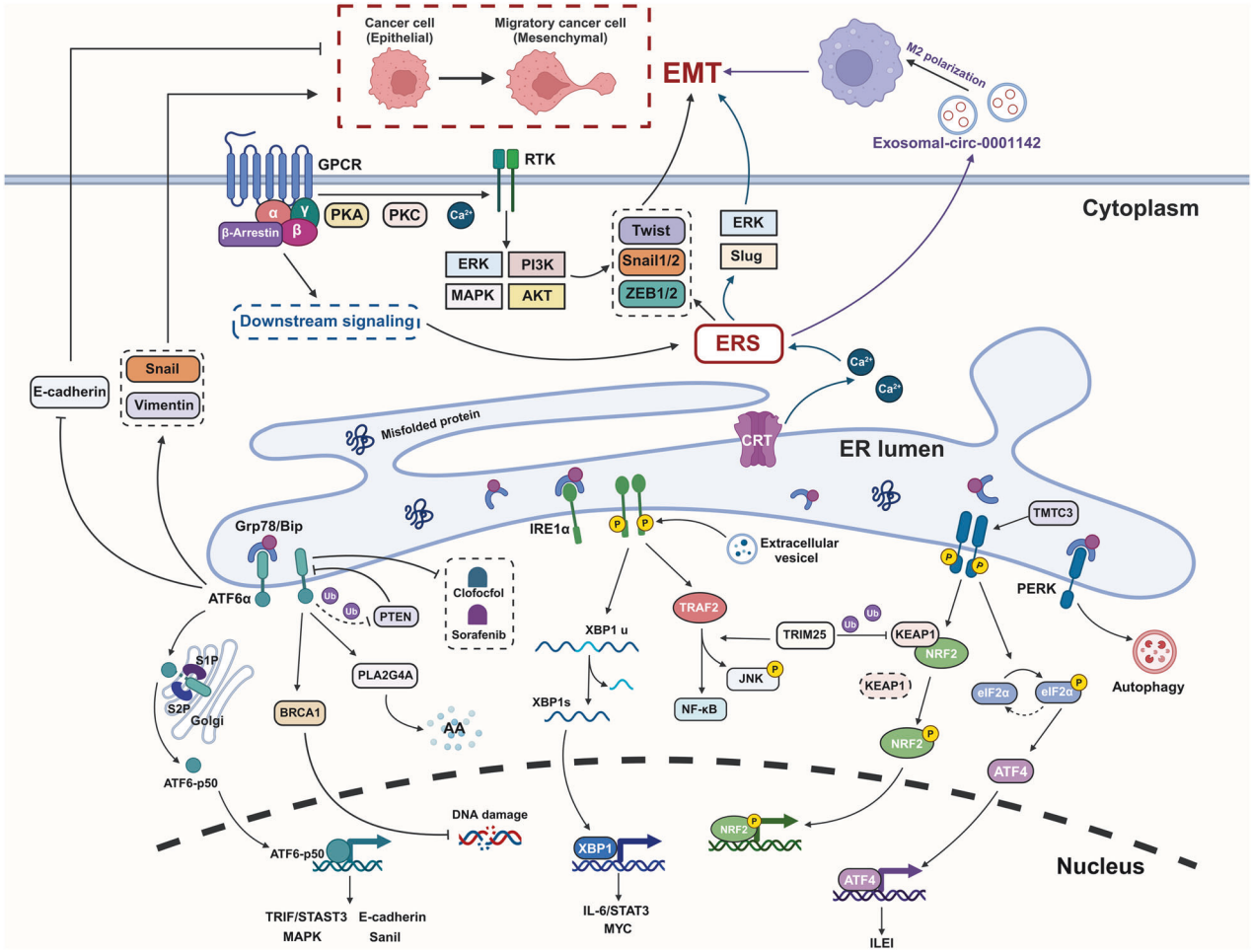

Fig. 3 The role of ERS in tumor growth, invasion, and metastasis. Growth: ERS regulates tumor growth through signaling pathways including IRE1/XBP1/IL-6/STAT3, IRE1/TRAF2/NF-κB, PERK/NRF2, PERK/eIF2α/ATF4, and ATF6/STAT3. Metastasis: ERS regulates tumor metastasis mainly through modulation of tumor cells EMT or polarization of tumor-associated macrophages.

inhibiting ERS often promotes the survival of UM cells [37]. This inhibitory effect may be related to ERS-associated autophagy. For instance, in breast cancer, PRL5 downregulates E2F1 expression, which in turn enhances the transcriptional activation of Bip/GRP78, suppresses the ERS response, and promotes autophagy [38]. Therefore, ERS-mediated autophagy is likely crucial for cell survival [39]. The primary objectives of autophagy are to rectify energy imbalances, ensure proper protein folding, and recycle cellular contents [40]. Generally, under ERS, the UPR detects the accumulation of misfolded proteins, leading to the activation of ATG genes (autophagy regulators) [41]. It is noteworthy that during this process, IRE1 and PERK are more significantly involved in stimulating autophagy [42]. In pancreatic cancer cells (PANC-1), fisetin induces protective autophagy by regulating the levels of IRE1, PERK, and ATF6 through the p8-p53/PKC-α pathway. Autophagy inhibitors CQ and 3-MA can enhance the anti-tumor effects of fisetin [43]. In gliomas, flavokawain B induces autophagy in GBM cells through the ERS-dependent ATF4–DDIT3–TRIB3–AKT–MTOR–RPS6KB1 signaling pathway to inhibit proliferation [44]. Similarly, combined treatment with autophagy inhibitors CQ proves to be an effective anti-tumor strategy in pancreatic cancer cells. ERS-related autophagy is also observed in lung adenocarcinoma, where interferon gamma (IFN-γ) induces ERS and UPR in lung adenocarcinoma cells by activating the JAK1/2–STAT1 and AKT–mTOR signaling pathways. IFN-γ-induced UPR subsequently reduces the expression of LAMP-1 and LAMP-2, impairing autophagic flux [45]. Additionally, DEH inhibits the growth of colorectal cancer cells by activating the PERK/eIF2α and IRE1α/XBP1s/CHOP pathways, thereby stimulating autophagy [46].

These findings highlight the role of ERS during cancer progression. The UPR's downstream branches exhibit divergent impacts across various malignancies, either as oncogenic drivers or suppressors, which were influenced by the intrinsic characteristics of the tumor and the interplay between the different branches of the signaling pathway. In addition, the functionality of ATF6 is complex and its paradoxical effects in prostate cancer may be related to the pharmacological agents used. Further investigation is needed to unravel the complex underlying mechanisms.

Apoptosis

Apoptosis operates as an inherent mechanism, aiding organisms in sustaining homeostasis within their internal environment. Conventionally, ERS serves a beneficial function, managing the synthesis and processing of a variety of proteins, including secreted and membrane-bound proteins. Nonetheless, during instances of prolonged or intense ERS, tumor cells inevitably encounter failure in re-establishing normal ER functions. This results in cellular dysfunction, ultimately triggering cell death.

It has been demonstrated that ERS can induce tumor cell apoptosis through the IRE1/TRAF2/ASK1/JNK pathway, the caspase-12 kinase pathway, and the C/EBP homologous protein (CHOP)/GADD153 pathway [47–52] (Fig. 4). Specifically, the caspase-12 pathway and the CHOP/GADD153 pathway may be

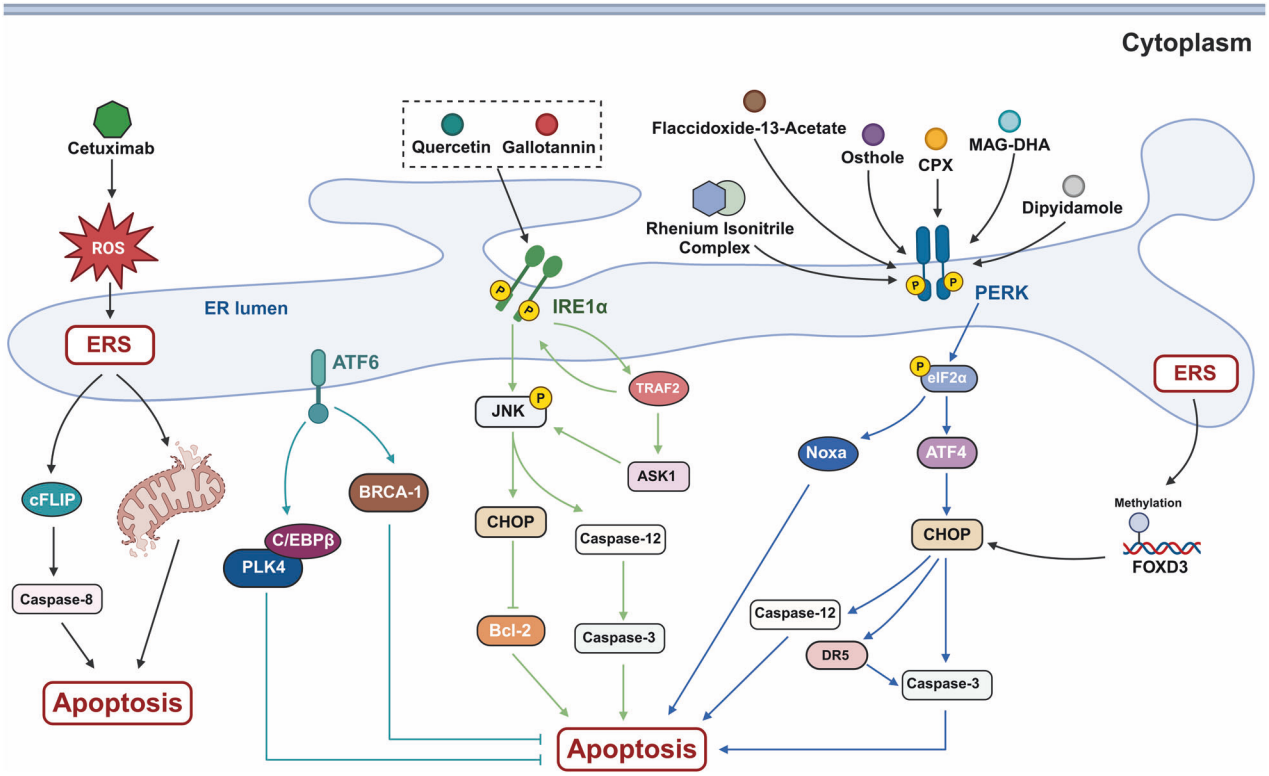

Fig. 4 Effect of endoplasmic reticulum stress on tumor cells apoptosis. IRE1 induce tumor cells apoptosis via IER1/TRAF2/caspase-12, IRE1/ASK1/JNK/BCL-2, and IRE1/JNK/BCL-2 signaling; PERK regulated tumor cells apoptosis via PERK/eIF2α/ATF4/CHOP/DR5/caspase-3 (caspase-12) signaling; ATF modulated apoptosis via ATF6/CHOP/DR5/caspase-3 (caspase-12) signaling.

delineated as IRE1/TRAF2/caspase-12 and PERK/ATF4/CHOP, respectively. These apoptotic signaling pathways may induce apoptosis by promoting the upregulation of downstream apoptotic effector protein caspase-3 [47, 49–52]. Additionally, ERS can suppress Bcl-2 expression via the IRE1–JNK–CHOP pathway, thereby inducing apoptosis in gastric cancer cells [53, 54]. The IRE1/TRAF2/ASK1/JNK cascade is initiated when IRE1 recruits TRAF2 to form the IRE1–TRAF2 complex. This subsequently activates apoptosis signal-regulating kinase 1 (ASK1), which in turn activates JNK, ultimately leading to apoptosis [47, 48]. The CHOP, a specific protein of ERS, is intrinsic to ERS and a member of the CCAAT/enhancer-binding proteins (C/EBPs) family. It is usually expressed at a minimal level. In the context of ERS, transcription factors such as ATF4, ATF6, and XBP1 translocate into the nucleus, where they enhance CHOP transcription. This ultimately leads to the activation of the apoptotic effector caspase-3, thus triggering tumor cell apoptosis [55]. Previous studies have demonstrated that quercetin can induce apoptosis in cervical cancer cells by activating the ERS response, although the precise mechanisms underlying this process remain unclear. Experimental data indicate that the levels of Bax, Bcl-2, GRP78, CHOP, and IRE1 increase in correlation with the concentration of quercetin [55]. This inference implies a potential linkage between apoptosis in cervical cancer cells and the IRE1–JNK–CHOP pathway, presenting a prospective novel therapeutic strategy for cervical cancer. In addition, shikonin may stimulate the death of gastric cancer cells via this pathway. Such an observation accentuates the importance of the IRE1/JNK/CHOP signaling axis in modulating tumor cell apoptosis [54].

In hypoxic conditions, osthole initiates the PERK/eIF2α/ATF4/CHOP/DR5 signaling cascade within the UPR, thereby upregulating the expression of caspase-3 and promoting apoptosis in colon cancer cells [56]. Similarly, docosahexaenoic acid monoglyceride (MAG-DHA) activates the PERK/eIF2α/CHOP pathway and upregulates the expression of the lytic enzyme caspase-12, thereby promoting apoptosis of breast cancer cells [57]. The PERK/eIF2α/ATF4 pathway also plays a role in cyclophosphamide-induced apoptosis in colorectal cancer cells. Furthermore, it has been demonstrated to promote apoptosis in chemoresistant (Hct-8/5-FU) and chemosensitive (Hct and DLD-1) colorectal cancer cells [58]. The methylation of FOXD3 under conditions of ERS results in the augmented expression of proteins associated with the UPR, followed by the upregulation of the CHOP protein, which consequently promotes apoptotic processes [59]. It is noteworthy that the downregulation of cFLIP represents a crucial early step in the ERS-induced apoptosis pathway in colorectal cancer cells [60]. In bladder cancer, flacidoxide-13-acetate induces apoptosis by activating the PERK/eIF2α/ATF6/CHOP signaling axis. Gamma-tocotrienol, on the other hand, promotes apoptosis by activating the PERK/eIF2α/ATF4 signaling pathway via ERS [61], it is reasonable to posit that apoptosis in bladder cancer cells may also be mediated through this pathway. Additionally, ERS-induced apoptosis has been reported in glioma cells [62, 63]. In glioma cell models U87 and T98G, dipyridamole induces apoptosis by regulating the PERK/eIF2α signal pathway to activate the BH3-only protein Noxa [51]. The PERK pathway-mediated apoptosis generally follows the PERK/eIF2α/ATF4/CHOP pathway, similarly demonstrated by $[Re(CO)_3(dmphen)(p\text{-tol-ICN})] + (TRIP)$-mediated cancer cell death [64]. Additionally, research on cetuximab-induced apoptosis in laryngeal squamous cancer cells indicates that ROS play a significant role in ERS-mediated apoptosis [65]. The findings provide insights for future investigations into ER-mediated tumor cell apoptosis. ER-induced apoptosis of tumor cells is also notably observed in neuroblastoma. Earlier studies with Hela cells demonstrated that fenretinide (4HPR) induces tumor cell death and procaspase activation via the PERK/eIF2α

signaling pathway [66]. Further research indicated that in neuroblastoma, fenretinide achieves its anti-tumor effects by inducing ERS, specifically through upregulating ATF4 transcription levels, thereby promoting apoptosis [67]. Protein disulfide isomerase (PDI) is a foldase and molecular chaperone essential for the formation, breakage, and rearrangement of disulfide bonds in unfolded or misfolded proteins, playing a critical role in maintaining ER protein homeostasis. Dysregulation of PDI can impair the protein-folding efficiency within the ER lumen, resulting in the accumulation of unfolded and misfolded proteins, which in turn triggers ERS [68]. Evidence has shown that PDI is overexpressed in breast cancer [69, 70]. DDA, a PDI inhibitor, has been demonstrated to induce breast cancer cell death in both in vitro (MDA-MB-468) and in vivo (BT474 mouse xenograft model) studies. The underlying mechanism may involve DDA targeting PDI family members, such as PDIA1, AGR2, and ERp44, thereby initiating DR4 and DR5-mediated caspase 8 and 3 activation, leading to apoptosis [71].

As a general rule, ERS can instigate apoptosis through several downstream signaling pathways. The most commonly implicated pathways involve IRE1 and PERK, whereas ATF6, frequently observed serving an anti-apoptotic role, is less prevalent. A multitude of studies have suggested that upon activation in osteosarcoma cells, ATF6 interacts with the polo-like kinase 4 promoter to enlist C/EBPβ, subsequently inhibiting apoptosis in these cells [72]. In colon cancer cells, it conserves the expression of BRCA-1, thereby shielding the cells from cytotoxic effects mediated by ER stressors such as DPE and thapsigargin (TG) [33].

Invasion and metastasis

The intricacies of tumor invasion and metastasis represent a complex phenomenon, with the underpinning mechanisms still largely elusive. Research has underscored the substantial influence of ERS not only on modulating tumor growth and apoptosis but also on governing tumor invasion and metastasis.

The invasion and metastasis of tumors mediated by ERS are influenced by multiple factors (Fig. 3). Initially, the process of invasion and metastasis of tumors is linked to ERS-regulated epithelial–mesenchymal transition (EMT), a transformation characterized by the reduction of epithelial markers and an increase in mesenchymal markers, which significantly contributes to the invasiveness of tumor cells [73]. Within ERS, the UPR collaboratively regulates EMT with G-protein coupled receptors (GPCRs), impacting tumor invasion and metastasis. GPCRs, upon binding to ligands with trimeric proteins and β-arrestin on the cellular membrane, initiate a cascade involving downstream UPR signals such as IRE1, PERK, and ATF6. Concurrently, through interactions involving PKA, PKC, calcium ions, and receptor tyrosine kinases, GPCRs facilitate the activation of pathways like ERK/MAPK and PI3K/AKT. These pathways, in concert with active ERS, upregulate the expression of EMT transcription factors (Snail1/2, Twist, and ZEB1/2), further activating EMT [74]. For instance, in a cervical cancer model, the ATF6 branch of UPR can promote EMT and further tumor invasion and metastasis by reducing the expression of E-cadherin and upregulating the expression of the major transcription proteins Snail and vimentin through the MARK signaling pathway [35]. In addition, calreticulin facilitates both acute and chronic free calcium-dependent ERS by activating the Slug and ERK signaling pathways and subsequently promoting EMT [75]. And ERS may enhance tumor invasiveness and metastasis by promoting the release of exosomes, which are specialized extracellular vesicles encapsulating diverse RNA molecules and proteins, generally 50–200 nm in diameter [76]. Research indicates that the CXCL12/CXCR4 axis is closely related to liver metastasis of colorectal cancer, and exosome-encapsulated miRNAs can promote this process by enhancing the polarization of M2 macrophages [77]. In breast cancer, ERS facilitates metastasis by inducing the release of exosome circ_0001142, which polarizes M2 macrophages [78].

In summary, ERS generally facilitates the migration of the majority of tumor cells. However, in certain tumors, such as epithelial ovarian cancer, it paradoxically exerts an inhibitory influence. The exact mechanisms behind this effect remain elusive, potentially tied to the distinct characteristics inherent to various tumor types.

Angiogenesis

Solid tumors are characterized by a microenvironment deficient in oxygen and nutrients due to the significant consumption necessitated by the rapid proliferation and invasive metastasis of tumor cells. This deficiency can be replenished via tumor angiogenesis. Under hypoxic conditions, ERS facilitates angiogenesis through the downstream pathway of UPR (Fig. 5). However, ERS does not universally promote angiogenesis. In certain contexts, it might suppress tumor vascular development, as exemplified when angiogenesis is inhibited by tumor-secreted exosomes induced by ERS [79, 80].

Hypoxia-inducible factor-1 (HIF-1), a key protein within the TME, is known for its role in promoting the transcription of molecules such as the vascular endothelial growth factor (VEGF) [81]. Studies have suggested that XBP1, a downstream molecule of the IRE1 pathway, can facilitate tumor angiogenesis independently of VEGF [82]. In model systems employing human umbilical vein endothelial cells, IRE1 knockdown significantly impairs HIF-1α protein expression under hypoxic conditions. This inhibition appears to primarily depend on the endonuclease activity of IRE1, rather than its downstream effector XBP1s [83]. Notably, in gliomas, IRE1 inhibition results in marked downregulation of angiogenesis-related molecules, principally those that are downstream targets of HIF-1. This could be attributed to IRE1's role in stabilizing HIF-1 protein [84]. Moreover, inhibiting IRE1α has been observed to reverse ERS adaptation, thereby enhancing the efficacy of anti-angiogenic therapies in triple-negative breast cancer [85]. The IRE1 pathway of the UPR collaborates with ANG-II to foster tumor angiogenesis. Specifically, Ang-II triggers the IRE1/JNK/P38 signaling cascade of ERS and concomitantly upregulates VEGF expression through interactions with its AT1R receptor [86, 87]. Recent findings show that salubrinal acid B, a novel type I IRE1 kinase inhibitor, suppresses angiogenesis by downregulating this pathway [88]. These insights underscore multiple mechanisms through which IRE1 fosters tumor angiogenesis.

In addition to IRE1 downstream factors XBP1 and HIF-1α, PERK downstream factors such as ATF4 and ATF6 have been shown to interact with vascular endothelial factor promoters, thereby augmenting their expression [89–91]. PERK has been implicated in promoting the expression of a plethora of angiogenic factors [92]. In gliomas, it has been demonstrated that the expression of peptidylglycine alpha-amidating monooxygenase mediated by PERK stimulates angiogenesis, thereby accelerating tumor growth [93]. Moreover, in pancreatic ductal adenocarcinoma (PDAC), cancer-associated fibroblasts (CAFs) can contribute to tumor microvasculature formation and subsequent tumor progression by serving as sources of endothelial cells. This is largely facilitated through the activation of the PERK–eIF2α–ERK1/2 signaling pathway in CAFs, driving the transition from mesenchymal to endothelial phenotypes and thereby promoting tumor vascularization [94]. Among the three primary downstream branches of the UPR, ATF6's role in fostering angiogenesis within tumors has been relatively underexplored.

Hence, ERS can either promote or hinder tumor angiogenesis, setting the stage for inventive therapeutic strategies that exploit ERS inhibition to boost anti-angiogenic responses. Furthermore, beyond the direct effects of ERS, tumor exosomes associated with this stress phenomenon can modulate angiogenesis, predominantly by inhibiting it.

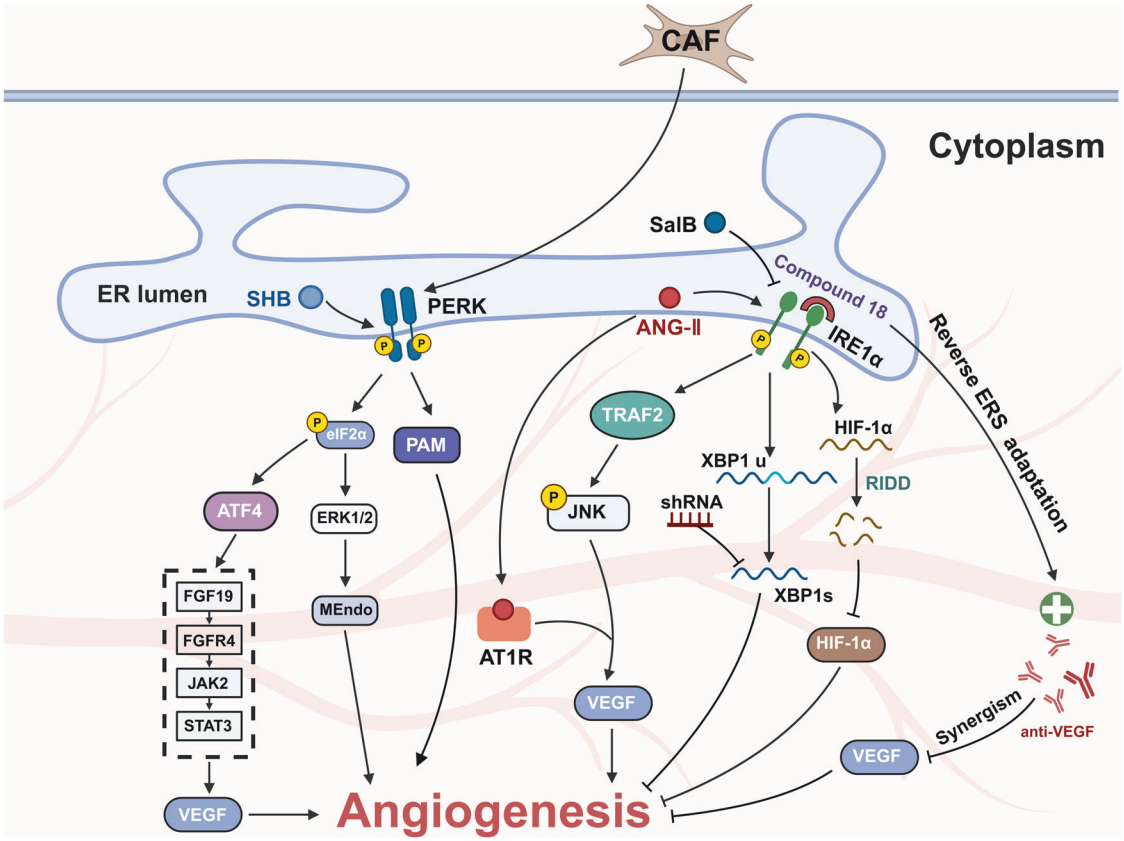

Fig. 5 The role of ERS in tumor angiogenesis. Endoplasmic reticulum stress (ERS) plays a pivotal role in the modulation of tumor angiogenesis via a myriad of interwoven pathways, encompassing IRE1α, PERK, BIP, ATF6, and the secretion of exosomes. Within the IRE1α signaling axis, certain molecules, such as SalB and ANG-II, have been implicated in either activating or repressing the angiogenic process. Along the PERK pathway, entities like SHB and cancer-associated fibroblasts (CAFs) facilitate angiogenesis through the manipulation of the PERK cascade. In contrast to these mechanisms, a reduction in BIP expression or the presence of tumor-derived exosomes tends to exert an inhibitory influence on angiogenesis regulation.

Drug resistance

Chemotherapy has long served as a cornerstone treatment for various cancers, yet its effectiveness can sometimes be suboptimal among certain patients. In addition to the notable side effects associated with chemotherapy, sustained treatment often leads to the development of drug resistance within tumor cells. Comparable challenges have emerged with recent advances in immunotherapies and targeted therapies. Consequently, a pivotal focus in clinical oncology research involves augmenting tumor cell susceptibility to chemotherapy and other therapeutic agents. Past investigations have delineated five mechanisms through which tumors may develop resistance: (1) reduced drug uptake; (2) genetic determinants (including gene mutations, amplifications, and epigenetic alterations associated with microRNAs); (3) augmented autocrine production of growth factors; (4) repair of drug-induced DNA damage; and (5) heightened metabolism of xenobiotics [95].

First, tumor drug resistance associated with ERS correlates with downstream pathways of the UPR. A previous study showed that ATF6 mediates chemotherapy resistance in cancer cells by promoting their survival [96]. Recent analyses of ERS and resistance in HCC have shown that ATF6 activated P58 via its protease activity [97]. For example, colorectal cancer patients initially positive for EGFR exhibited significant sensitivity to cetuximab, yet ultimately developed resistance [98]. Carfilzomib, targeting K-RAS(+) and cetuximab-resistant colorectal cancer, operates by upregulating UPR downstream CHOP and ATF6 expression, and enhancing apoptotic pathways through caspase-3/7 for anti-tumor activity [99]. It has been demonstrated that ATF6 sustains activation of the mammalian target of rapamycin (mTOR) pathway, a vital element in tumor metabolism [100]. Further research underscores the crucial role of ATF6 in DNA repair, which is achieved by maintaining BRCA-1 expression in colon cancer cells under ERS. This subsequently elevates sensitiveness to doxorubicin by intensifying the cytotoxic effects of ERS-inducing drugs [33]. This underscores the potential of ATF6-targeted therapies as novel chemosensitizers in colorectal cancer treatment. Earlier research on the PERK pathway revealed that PERK induces tumor drug resistance by upregulating ABC transporters or activating Nrf2 to stimulate autophagy [96]. For example, in chemoresistant human colorectal adenocarcinoma HT29 cells, both ABCC1 and Nrf2 are upregulated [101]. Present studies indicate that PERK primarily enables drug resistance through the PERK–eIF2α–ATF4–CHOP pathway by activating autophagy [97]. In the IRE1 pathway, phosphorylated IRE1 upregulates ABC transporter expression, inhibiting cell cycle arrest and apoptosis, thereby fostering drug resistance, or by altering drug transport via splicing XBP1 and activating Nrf2 [96]. This is specifically exemplified in colorectal cancer, where 5-FU activation of the XRE1–ABCB1–XBP1 pathway enhances ABC protein expression, promoting resistance to fluorouracil [102]. And new resistance mechanisms involving IRE1, such as the IRE1–TRAF2–JNK pathway enhancing DNA repair and inhibiting apoptosis, as well as affecting drug transport by splicing XBP1 and activating Nrf2, have been proposed [97]. In certain cancer types, drug resistance is orchestrated through the modulation of the IRE1 and PERK signaling pathways. Notably, triple-negative breast cancer

Table 1. Representative drugs that induce tumor sensitivity or resistance via ERS.

Pharmaceutical	Targets	Mechanism	Tumor	References
Carfilzomib	ATF6	CHOP, ATF6 caspase-3/7↑	Colorectal cancer	[99]
5-FU	IRE1	IRE1–ABCB1–XBP1	Colorectal cancer	[102]
5-FU	PERK	ABCC1↑, Nrf2↑	Colorectal cancer	[101]
Doxorubicin	ATF6	Cytotoxic effect	Colorectal cancer	[33]
Doxorubicin	IRE1, PERK	PDCD4–eIF4A–FAK pathway	Triple-negative breast cancer	[103]
Sorafenib, sunitinib, gefitinib	GRP78/BIP	Unclear	Hepatocellular carcinoma Renal cell carcinoma Non-small cell lung cancer	[108–110]
Gemcitabine	GRP78/BIP	CLPTM1L/CRR9	Pancreatic cancer	[110]
Ibrutinib	IRE1	IRE1/XBP1	Diffuse large B-cell lymphoma	[120]
Trastuzumab	Unclear	miR-301a-3p	HER2-positive gastric cancer	[117]
Cisplatin Cisplatin	Unclear IRE1,PERK	miR-512-3P NF-κB	Retinoblastoma Osteosarcoma	[118] [104]
Cisplatin	GRP78/BIP	Exosomal ERp44	Nasopharyngeal carcinoma	[112]
Cisplatin	GRP78/BIP	ATM pathway and calcium efflux	Ovarian cancer	[113, 114]
Gemcitabine	Unclear	PGM3↓	Pancreatic cancer	[119]
Imiquimod	Unclear	miR-410-3p	Melanoma	[107]
Tamoxifen	Bip/GRP78	Unclear	Breast cancer	[170]

exhibits resistance to doxorubicin, and osteosarcoma demonstrates resistance to cisplatin, among others [103, 104]. In melanoma, activating mutations in BRAF induce persistent ERS [105]. The resistance to most anti-cancer therapies is attributed to the adaptation to prolonged low-intensity ERS. For instance, this resistance is mediated by the activation of NFκB and the inhibition of apoptosis proteins via the IRE1α/TRAF2 pathway [106]. Another instance of resistance in melanoma involves vemurafenib, which induces miR-410-3p in melanoma cells through ERS. This induction promotes the transition of cells to a more invasive phenotype, resulting in resistance to BRAF inhibitors [107].

Furthermore, the resistance or sensitivity of tumor cells to therapeutic agents may be associated with BiP/GRP78, a chaperone protein that binds to monomers downstream of the UPR and stabilizes IRE1, PERK, and ATF6. It has been extensively documented that overexpression of GRP78 contributes to resistance in various cancers, such as sorafenib resistance in liver cancer [108], sunitinib resistance in renal cancer [109], and gefitinib resistance in NSCLC [110]. In pancreatic cancer models, GRP78-mediated chemotherapy resistance arises from its interaction with the extracellular domain of CLPTM1L/CRR9 on tumor cell surfaces. This interaction can be targeted by monoclonal antibodies against CLPTM1L/CRR9, enhancing chemotherapy sensitivity and unveiling a novel therapeutic approach [111]. BiP/GRP78 can also regulate nasopharyngeal carcinoma resistance to cisplatin through the modulation of exosome ERp44 [112]. Additionally, a distinctive aspect observed in cervical cancer models is that overexpression of GRP78 in cervical cancer (CVC) exhibits dual influences on cisplatin responsiveness, affecting both resistance and sensitization [113, 114]. These examples underscore the pivotal role of BiP/GRP78 in conferring resistance to chemotherapeutic and immune-targeted drugs, with targeting BiP/GRP78 emerging as a promising strategy for enhancing cancer treatment. Of course, there are many more mechanisms of tumor cell resistance mediated by ERS, including the role of hydroxymethylglutaryl-CoA synthase 1 in promoting resistance in acute myeloid leukemia through the ER–UPR–mitochondrial axis [115]. ERS-induced downregulation of PHLPP leads to chemotherapy resistance in colon cancer [116], and ERS-induced upregulation of exosome miR-301a-3p causes resistance in HER2-positive gastric cancer cells to trastuzumab [117].

Moreover, ERS does not invariably enhance tumor resistance to therapeutic agents; it can also substantially boost sensitivity by aiding some tumors in overcoming resistance. Part of this mechanism is closely related to ERS-induced apoptosis of tumor cells. For example, recent research indicates that exosome miR-512-3p has facilitated retinoblastoma cells in overcoming cisplatin resistance by promoting apoptosis triggered by ERS [118]. Numerous instances exist, such as the inhibition of phosphoglucomutase 3 (PGM3) activating UPR to counteract gemcitabine resistance in pancreatic cancer [119], and the activation of the IRE1–XBP1 pathway of UPR overcoming ibrutinib resistance in diffuse large B-cell lymphoma [120] (Table 1).

Taken together, ERS plays an extremely important role in various cancer drug therapies, and the mechanisms by which different UPR signals affect tumor drug resistance are not the same. Notably, even a singular pathway can have profoundly disparate impacts on either enhancing sensitivity or fostering resistance to drugs in tumor cells. Thus, further exploration into the role of ERS in modulating tumor resistance could unveil novel strategies for overcoming drug resistance in cancer.

Glycolysis and lipid metabolism

Normal cellular metabolism plays a pivotal role in maintaining physiological functions. In cancer cells, due to the demands of rapid growth and invasive metastasis, metabolic activities are abnormally amplified to support their proliferative needs. Concurrently, the accumulation of metabolic waste can negatively impact the growth of these cells. As a result, ERS aids cancer cells in adapting to various hostile environments, thus promoting their survival (Fig. 6).

Initially, ERS modulates glycolysis in a variety of cancer cells to control tumor growth. For example, in PDAC, BZW1 is overexpressed and functions as an adapter of PERK, facilitated eIF2α phosphorylation. This activation promoted internal ribosome entry site-dependent translation of HIF-1α and c-Myc, stimulating the Warburg effect and accelerating PDAC cell proliferation [121]. In addition, ERS-dependent upregulation of ERO1L also facilitates the Warburg effect, thereby promoting PDAC growth [122]. Treatment

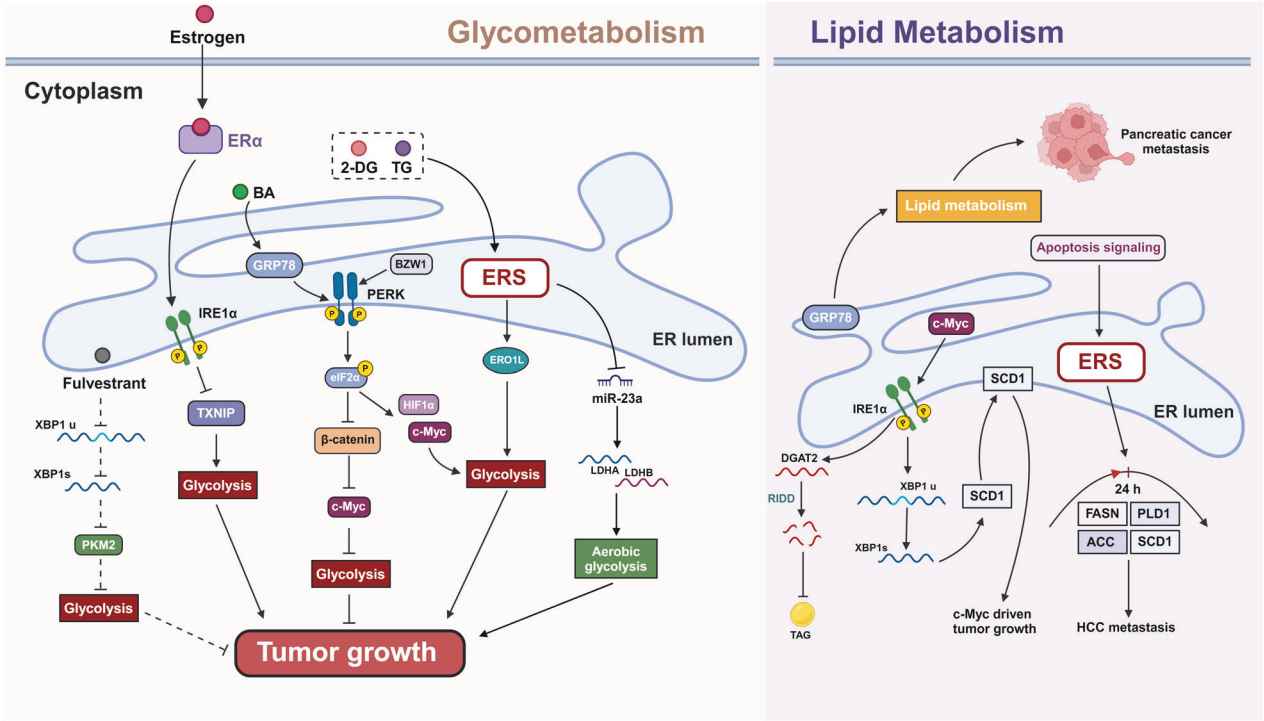

Fig. 6 Effects of endoplasmic reticulum stress on glycolysis and lipid metabolism. Glycolysis: in tumor cells, glycolysis may be modulated by ERS-induced UPR, miRNA, or mitochondrial dysfunction. Specifically, the upregulation of BZW1 and overexpression of ERO1L promote pancreatic ductal cancer cell glycolysis through PERK. BA induces overexpression of GRP78 and activates the PERK pathway, subsequently downregulating β-catenin expression. This series of events leads to c-Myc-mediated glycolytic inhibition, thereby suppressing breast cancer cell proliferation. Estrogen enhances glycolysis and orchestrates the proliferation of breast cancer cells by decreasing the expression of TXNIP via activation of the IRE1/XBP1 pathway. The anti-proliferative effect of fulvestrant on prolactinoma GH3 cells is achieved by activating IRE1, reducing PKM2 expression, and inhibiting glycolysis. Lipid metabolism: ERS typically affects lipid metabolism through IRE1, PERK, and GRP78/BIP. IRE1 can augment SCD1 expression or mediate RIDD to reduce DGAT2 mRNA expression, thereby impacting lipid metabolism. The PERK pathway can influence lipid metabolism by controlling the expression of lipid regulatory enzymes such as FASN, ACL, and SCD1. Conversely, GRP78/BIP regulates lipid biosynthesis by modulating SREBP.

of HeLa cells with the glucose analog 2-deoxyglucose or TG induces ERS, promotes LDHA and LDHB expression by inhibiting miR-23a, thus adapting the cells to aerobic glycolysis and enhancing tumor proliferation [123]. In addition, the ERS receptor Bip/GRP78 plays a critical role in pancreatic cancer by modulating the oxidative state of cells to maintain tumor stem cell stability [124]. In highly invasive breast cancer, betulinic acid induces Bip/GRP78 overexpression and activates PERK, leading to eIF2α phosphorylation, which inhibits β-catenin expression and subsequently represses c-Myc-driven glycolysis [125]. And estrogen enhances the Warburg effect in breast cancer by activating the IRE1 signaling pathway of the UPR to suppress TXNIP expression, elucidating the pathway by which the estrogen/ERα–IRE1–TXNIP axis stimulates tumor cell growth and proliferation [126]. Low expression of XBP1, including XBP1s and XBP1u (downstream targets of IRE1), can inhibit the Warburg effect in prolactinoma GH3 cells by downregulating PKM2, and fulvestrant exerts its tumor-suppressive effects through this pathway [127].

Second, in addition to glycolysis, alterations in lipid metabolism are a major hallmark of cancer [128]. In tumor cells, ERS affects not only glycolysis but also lipid metabolism. It is well documented that lipid metabolism in tumor cells is closely linked to the IRE1 signaling pathway. For example, in tumors transformed by c-Myc, IRE1α/XBP1s stimulates tumor growth by upregulating the expression of the lipid desaturase SCD1, a key enzyme in lipid metabolism and tumor invasion located in the ER [129, 130]. In addition, studies suggested that IRE1α, through its role in regulated IRE1-dependent decay (RIDD), acts as a transcriptional repressor of DGAT2 expression in cells such as MDA-MB-231, HCC1806, and BT-549, resulting in reduced DGAT2 mRNA levels and subsequently lower triacylglycerol levels [131]. Apart from the IRE1 pathway, tumor lipid metabolism is intricately linked to the PERK pathway. Prior research has demonstrated that dysfunction in the PERK pathway leads to reduced expression of fatty acid synthesis enzymes like FASN, ACL, and SCD1, highlighting the link between PERK and the regulation of lipid metabolism [132]. In studies using the HepG-2 liver cancer model, apoptin-mediated ERS was found to drive changes in lipid metabolism, increasing the expression of lipid synthesis-related enzymes such as FASN, ACC, PLD1, and SCD1 within the first 24 h, followed by a decline [133].

This emphasizes the influence of ERS on lipid metabolism, suggesting that sustained stress may result in a diminution of lipase levels due to ER injury, consequent enzyme downregulation. Moreover, apoptin has been demonstrated to inhibit the invasion and metastasis of HepG-2 liver cancer cells, thereby presenting a new avenue for research. In summary, ERS imposes diverse effects on glycolysis and lipid metabolism within tumor cells, subsequently modulating their growth as well as the processes of invasion and metastasis.

Immunity response

In certain adverse tumor environments, including nutrient deprivation, hypoxia, accumulation of inhibitory metabolites, and abnormal production of ROS, the ER balance within tumor-associated immune cell subsets is disrupted, leading to compromised anti-tumor immune responses [134] (Fig. 7). ERS induced by the TME is a major factor in the dysfunction of tumor-infiltrating T cells [135, 136], which was mainly achieved through the activation of IRE1, PERK, and CHOP driven by the TME [137–139].

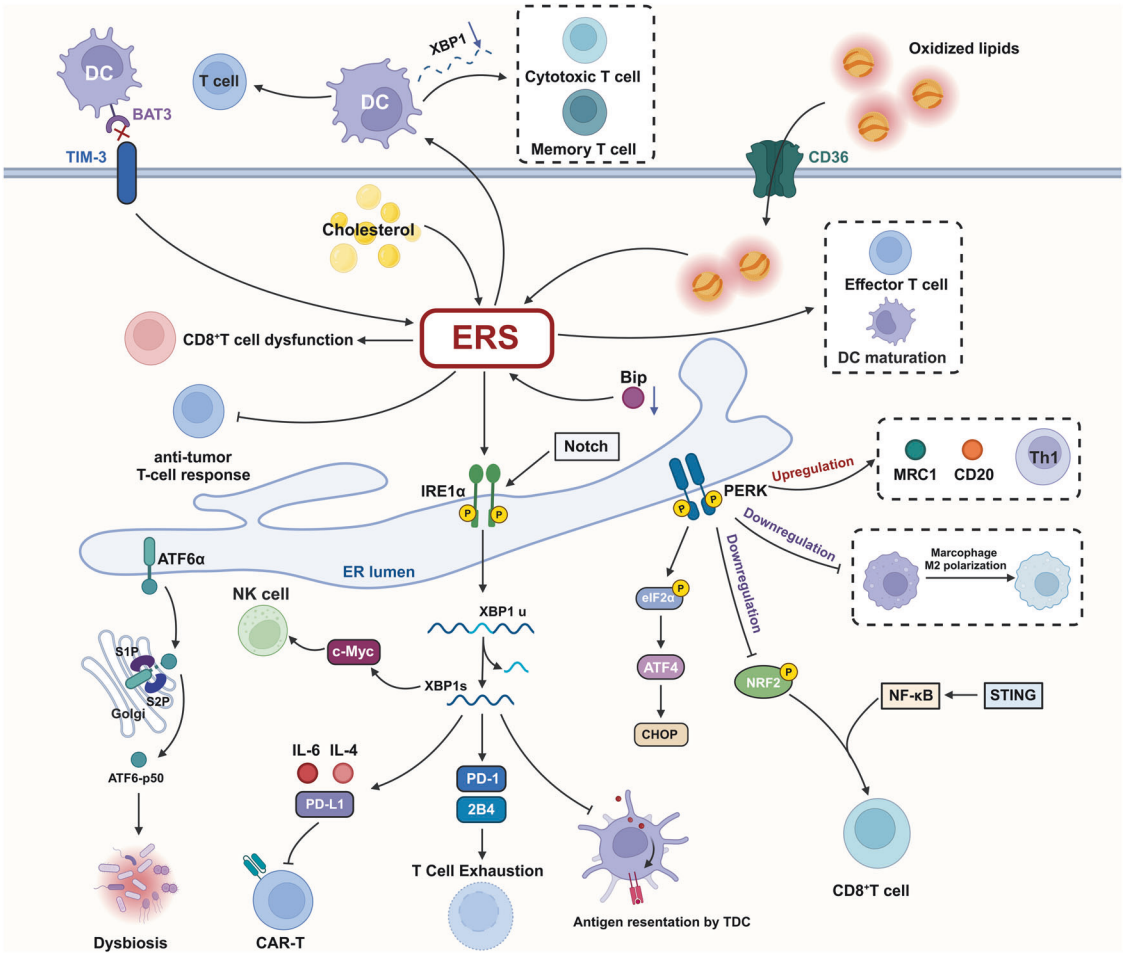

Fig. 7 The role of ERS in tumor immunity. In tumor-associated immunity, the IRE1 arm not only suppresses T cell activity and proliferation, but also inhibits the antigen presentation capacity of dendritic cells (DC) and the proliferation of natural killer (NK) cells. The PERK arm, through its signaling pathway, can influence the expression of macrophages, DC, and T helper (Th) cells, and also plays an immunosuppressive role in myeloid-derived suppressor cells (MDSCs). Furthermore, ATF6 primarily mediates the occurrence of innate immunity in the intestine.

It was shown that accumulation of cholesterol by CD8+ T cells in the tumor-induced expression of the inhibitory receptors PD-1 and 2B4 and promoted T cell exhaustion in an XBP1-dependent manner. Conversely, XBP1 deficiency enhanced T cell anti-tumor function and prolonged patient survival [139, 140]. And CD36-mediated uptake and oxidation of low-density lipoprotein progressively induces severe ERS in T cells, which is a major cause of CD8+ T cell dysfunction [141, 142]. In certain cancers, such as uveal melanoma, CD8+ T cell infiltration levels correlate strongly with a higher risk of disease. Reports indicate that high-risk uveal melanomas show increased infiltration of CD8+ T cells, follicular helper T cells, gamma and delta T cells, and activated NK cells, while low-risk cases show a greater presence of memory resting CD4+ T cells, naive B cells, activated and resting mast cells, monocytes, and resting NK cells [143]. The mechanism may be that in CD8+ T cells, ERS and the UPR act as extracellular immune regulators, modulating dendritic cells (DCs) through polarization types and pro-inflammatory responses, thereby promoting the production of under-proliferating T cells [144]. A study had elucidated a potential mechanism by which DCs deficient in the adapter protein BAT3, which interacts with TIM-3 on T cells, exhibit a hyperactive UPR, leading to the development of a tolerogenic phenotype that subsequently attenuates the efficacy of anti-tumor T cell responses [145]. Furthermore, tumor DCs with inactivated XBP1 can enhance the functionality of lymphocytes, such as the maturation of cytotoxic T lymphocytes and memory T lymphocytes [146]. Additional research on diffuse large B-cell lymphoma demonstrates that in myeloid macrophages, activation of the Notch-1/IRE1/XBP1s pathway promotes the secretion of IL-6, IL-4, and PD-L1, thereby suppressing the functionality and proliferation of CAR-T cells and facilitating their apoptosis [147]. The mechanisms by which ERS affects tumor-associated DCs have also been elucidated, where changes in the TME leading to the accumulation of unfolded protein induce the activation of ERS and IRE1α–XBP1 signaling, thereby inhibiting their antigen-presenting function [148, 149]. These examples highlight the significant influence of the IRE1–XBP1 axis within ERS on tumor-related immune cells. Moreover, tumor-associated macrophages (TAMs), a predominant myeloid cell population in numerous cancers, exhibit increased XBP1 splicing in TAMs isolated from colorectal cancer patients compared to peripheral monocytes or macrophages [150]. The PERK pathway also influences the functionality of TAMs, as evidenced in the B16-F10 melanoma model, where PERK-deficient macrophages show impaired M2 polarization [151]. This illustrates the critical role of ERS in TAMs. The role of PERK in tumor immunity extends beyond this; a GSEA result indicates that PERK is primarily enriched in immune-related signaling pathways in breast cancer (BRCA), thyroid cancer, and head and neck squamous cell carcinoma (HNSSC). Furthermore, PERK expression correlates closely with infiltrating macrophages, DCs, and immune

markers like macrophage mannose receptor 1 (MRC1, CD206), as well as T helper cells (Th) [152]. In the context of tumor-associated myeloid-derived suppressor cells (tumor-MDSCs), the downregulation of PERK transforms these cells into myeloid cells that activate CD8+ T cell-mediated anti-cancer immunity, featuring compromised NRF2-driven antioxidant capabilities and disrupted mitochondrial respiratory balance. This immune regulation is orchestrated through the STING pathway, with the abrogation of STING ameliorating the immune activation caused by PERK deficiency in tumor-MDSCs [153]. The fundamental mechanism involves STING's ability to modulate NF-κB activity, a pivotal factor in the functionality of tumor-MDSCs [154].

In tumor response, the impact of ERS on tumor immunity also involves NK cells. As a downstream effector of the mTOR signaling pathway, IRE1–XBP1 regulates the proliferation of NK cells by targeting c-Myc [155]. Certainly, as a UPR effector protein, ATF6 plays a role in tumor-associated immune responses, and in the absence of inflammation, ATF6 activation in colon epithelial cells promotes intestinal dysbiosis and innate immune responses, leading to microbiota-dependent tumor formation, although the exact mechanism remains to be investigated [34]. In the UPR process, the immunoglobulin-binding protein BIP is crucial in tumor-associated immune dynamics. Downregulation of BIP through phosphorylation of PERK and IRE1 stimulates the generation of damage-associated molecular patterns in response to radiation-induced ERS, facilitating DC maturation and effector T lymphocyte activation. In addition, BIP gene knockout combined with irradiation of glioma stem cells effectively prevents tumor development and reduces tumor recurrence after radiotherapy [156].

DISCUSSION AND PROSPECTS

The ER is a cellular component responsible for protein synthesis, and it induces ERS when its surrounding environment is disrupted or its function is impaired, disrupting the state of balance. ERS is widely associated with various human diseases, including neurodegenerative diseases, diabetes, cardiovascular diseases, inflammation, and cancers [19–21]. Pertinently, in cancer, ERS serves as a vital signal transduction pathway determining the fate of cancer cells, affecting their survival, metastasis, and resistance to therapy [157–159]. The TME is a process of polymorphic changes, such as hypoxia, glycation, and the accumulation of acidic substances, all of which can easily induce ERS [6, 7]. ERS broadly manifests through three principal pathways: the UPR, the endoplasmic overload response, and the sterol regulatory element-binding protein (SREBP) cascade. These mechanisms are instrumental in maintaining cellular homeostasis under stress conditions [8]. In tumor cells, the principal pathway involved is UPR, primarily orchestrated by IRE1, PERK, and ATF6. These three transmembrane proteins, located on the ER membrane, play distinct roles in manipulating tumor survival and development, alternately promoting or inhibiting tumor growth across different human tumors. Furthermore, the upregulation of ER-resident proteins and folding enzymes under stress conditions bolsters the ER's protein-folding capacity, thereby alleviating the load of unfolded proteins within the ER lumen.

Numerous studies have shown that the UPR can promote the proliferation of tumors such as liver cancer, melanoma, and breast cancer through various signaling cascades such as IRE1/XBP1/JNK, IRE1/XBP1/IL-6/STAT3, and IRE1/TRAF2/NF-κB [23, 24, 28, 29]. In the context of ERS-mediated tumor regulation, the role of IRE1 emerges as particularly significant. This includes promoting the proliferation of breast cancer cells via its IRE1–XBP1 pathway [26]; mediating tumor cell apoptosis through the IRE1/TRAF2/ASK1/JNK pathway [47, 48], controlling IRE1 signaling via GPCRs and subsequently activating EMT to foster tumor metastasis [74]; or promoting tumor invasion through the IRE1–XBP1 pathway, reflecting the multifaceted role of IRE1 in tumor development. Similarly, PERK's mechanism closely aligns with IRE1, though it may inhibit tumor proliferation, as evidenced in breast cancer [30]. ATF6 is mainly manifested in the acquisition of tumor resistance or sensitization, where it can promote tumor resistance via P58 [97], or act downstream of carfilzomib, achieving tumor resistance in patients resistant to cetuximab [99]. Additionally, ATF6's role in promoting microbiome-dependent tumor formation through intestinal flora imbalance and innate immune responses [34], or facilitating prostate cancer progression via the ATF6α–PLA2G4A pathway affecting arachidonic acid metabolism [31], highlights its varied implications in cancer dynamics, albeit its limited reported involvement in angiogenesis, similar to PERK. Within the context of ERS, Bip/GRP78 functions as a critical chaperone protein, impacting tumor energy metabolism not only by directly modulating the expression of various metabolic regulators but also by displaying dual characteristics that augment both sensitization and resistance. While certain mechanisms have been elaborated upon, others remain enigmatic, such as whether Bip/GRP78 operates through the three downstream branches of the UPR or if additional cascading pathways are involved. Are there more exosomes that can regulate tumor cell resistance to immune agents? These questions continue to pose challenges. Throughout the various stages of tumor development influenced by ERS, it's worth contemplating the cascading signals for tumor cell apoptosis elicited by ERS: (1) IRE1/TRAF2/ASK1/JNK pathway; (2) IRE1/TRAF2/caspase-12; (3) PERK/ATF4/CHOP; (4) IRE1–JNK–CHOP; (5) PERK/eIF2α/ATF4/CHOP/DR5; and (6) PERK/eIF2α/ATF4/CHOP/DR5 and other apoptotic pathways. These pathways predominantly achieve the induction of various tumor cell apoptosis by triggering the expression of caspase-3/7/9 or suppressing the expression of anti-apoptotic protein families. Hence, elucidating more about the mechanisms by which ERS incites tumor cell apoptosis is of paramount importance, with studies focusing on such pathways offering invaluable therapeutical targets. For instance, the P97 inhibitor CB-5083 activates the IRE1–XBP1s–CHOP pathway, promoting apoptosis in osteosarcoma cells [160]. In the treatment of neuroblastoma, resveratrol has been shown to trigger ERS-mediated intrinsic apoptosis in neuroblastoma cells and inhibit rho-dependent migration, thereby extending patient survival [161]. Recent studies have further demonstrated that fenretinide is an effective therapeutic option for neuroblastoma [162]. Beyond neuroblastoma, fenretinide also exhibits its anti-tumor effects by inducing apoptosis in head and neck squamous cell carcinoma through the upregulation of the pro-apoptotic protein NOXA via ERS [163]. These findings underscore the broad-spectrum anti-cancer properties of fenretinide. This highlights the potential of targeting ERS-induced apoptosis as an efficacious cancer treatment strategy.

Furthermore, ERS is pivotal in cancer cell survival, proliferation, and treatment resistance. Targeting ERS pathways, particularly the UPR mediated by IRE1, PERK, and ATF6, offers a novel therapeutic approach. As noted, IRE1 and PERK signaling are critical for RMS cell survival, with IRE1 inhibitor MKC8866 and PERK inhibitor AMGEN44 inducing senescence in rhabdomyosarcoma cells to curb proliferation. Therefore, developing RMS-targeted therapies using MKC8866 and AMGEN44 could be effective [164]. PDI family members are overexpressed in various cancers [165], and PDI dysfunction induces ERS, as previously discussed. For example, in PDAC cells, the PDI inhibitor E64FC26 induces ERS, disrupting protein homeostasis and leading to lysosomal defects. These defects limit apoptosis and ferroptosis induced by E64FC26-triggered ERS. Moreover, lysosomal defects prevent the formation of autophagolysosomes, resulting in autophagic cell death in PDAC cells [166]. Various PDI inhibitors, including LOC14 [167], securinine [168], and DDA [71], exhibit different effects across cancers, many closely linked to ERS, making them crucial targets for future development. ERS significantly contributes to tumor

drug resistance. For instance, in EGFR(+) colon cancer patients resistant to cetuximab, carfilzomib can enhance apoptotic signaling through ERS, serving as a viable alternative to cetuximab [99]. Furthermore, the overexpression of Bip/GRP78 in cervical cancer cells results in cisplatin resistance, underscoring the therapeutic potential of targeting ERS in cancer treatment. Future research should aim to optimize these therapies and overcome potential resistance mechanisms [113]. In relation to the interplay between ERS and autophagy in tumor cells, this topic has been previously discussed. Clinically, chloroquine and its derivative hydroxychloroquine (HCQ) are the only autophagy inhibitors approved for use. Clinical studies have indicated that HCQ can overcome chemotherapy resistance in various tumor cell lines and animal cancer models [169]. Cook et al. showed that in a breast tumor rat model, Bip/GRP78 promotes acquired resistance to tamoxifen in tumor cells [170]. In ERα-positive breast cancer cell lines, combined treatment with HCQ and tamoxifen exhibited superior efficacy compared to endocrine monotherapy [171]. Other instances include apatinib inducing ERS-mediated apoptosis and autophagy in esophageal squamous cell carcinoma via the IRE1α–AKT–mTOR pathway, enhancing cell sensitivity to paclitaxel, and being used in combination with CQ [172]. These findings highlight the role of autophagy inhibitors in overcoming tumor resistance and sensitivity, suggesting that autophagy inhibitors represent a promising strategy for anti-cancer therapy.

Alterations in the tumor cell microenvironment and inherent stemness under ERS remain largely unexplored, necessitating urgent attention. Moreover, some crucial and complex issues persist unresolved, such as whether other chaperone molecules besides Bip might play a role in initiating the UPR pathway. A more comprehensive examination of the interactions and influences of the UPR's tripartite branches IRE1, PERK, and ATF6 on tumor biological behaviors, including growth, invasion, metastasis, and angiogenesis, is imperative. Notably, these pathways often regulate tumor dynamics via downstream STAT3 signaling, underscoring the importance of exploring STAT3's role in tumor pathology as a promising research direction. Additionally, the pressing need to develop new therapeutic targets countering ERS in cancer treatment cannot be overstated. Fortuitously, several strategies targeting ERS, such as GlaxoSmithKline's PERK inhibitor GSK2656157 and the IRE1 activator IXA4/6, are already underway [173, 174]. Advancing the specificity of ERS's regulatory influence on tumor biology remains a pivotal area for future exploration. Prospective studies should aim to systematically elucidate the role of ERS in tumor tissues, emphasize the effects of ERS-mediated signaling pathways on diverse tumor biological behaviors, and innovate targeted therapies based on ERS and its downstream mediators.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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