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Review Article

Endoplasmic reticulum stress in non-small cell lung cancer

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Abstract: The Endoplasmic reticulum (ER), an organelle present in various eukaryotic cells, is responsible for protein synthesis, modification, folding, and transport, as well as for the regulation of lipid metabolism and Ca^{2+} homeostasis. ER stress plays a pivotal role in the pathogenesis and therapeutic response of non-small cell lung cancer (NSCLC), significantly influencing cellular fate decisions through its unique sensing and regulatory mechanisms. This review aims to elucidate the key role of ER stress sensors and to explore how they mediate cell autophagy, apoptosis, and non-apoptotic modes of cell death in the context of drug-treated NSCLC. This investigation lays a solid foundation for optimizing future treatment strategies for NSCLC.

Keywords: Endoplasmic reticulum stress, unfolded protein response, non-small cell lung cancer, autophagy, cell death

Introduction

Non-small cell lung cancer (NSCLC)

According to the Global Cancer Statistics 2020, lung cancer remains the leading cause of cancer-related deaths, accounting for 18% of total deaths from all malignancies globally [1-3]. NSCLC comprises the vast majority of lung cancers, approximately 85%, with 30% of patients presenting with locally advanced (Stage III) disease at the time of diagnosis. Clinically, the prognosis for NSCLC has consistently been poor, with a 5-year survival rate of only 15.9% [4-6]. Historically, definitive surgery was the primary treatment for early-stage NSCLC patients; however, 25-70% of these patients ultimately experience recurrence following complete resection [7]. For patients with advanced NSCLC, surgical intervention is often not feasible, leading to the use of platinum-based chemotherapy as the standard treatment in clinical practice. Nevertheless, chemotherapy lacks specificity in targeting cancer cells, resulting in a range of adverse reactions [8-11]. Therefore, it is crucial to identify the molecules responsible for the development and progression of NSCLC to facilitate the early discovery and development of new molecular targeted therapies.

Endoplasmic reticulum (ER) stress

The ER is a perinuclear organelle found in all eukaryotic cells, where one-third of human proteins are folded and assembled to attain their native conformation. These proteins are subsequently transported to various secretory environments, including lysosomes, the plasma membrane, and the extracellular space, to perform their full functions [12, 13]. Additionally, the ER plays a crucial role in regulating lipid, and steroid metabolism, as well as calcium homeostasis. It contributes to cellular homeostasis through the ER quality control system (ERQC), which prevents protein aggregation by either facilitating the correct folding of misfolded peptides or triggering their selective degra-

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Table 1. Differences in ER stress between normal cells and tumor cells

Difference	Normal cells	Cancer cells	Reference
Reason for activation	Physiological factors such as transient hypoxia, mild oxidative stress, nutritional fluctuations, cellular differentiation, and circadian rhythms.	Pathologic factors such as hypoxia, low glucose, growth factor deficiency, lactic acidosis, oxidative stress, and amino acid starvation.	[19-22]
Duration	ER stress duration is generally transient, but may be continuously activated during certain physiological activities as a means of fine-tuning cellular conditions in real time, such as circadian rhythms.	Sustained activation.	[19, 22]
Result of activation	Maintain cellular homeostasis and initiate apoptotic program to remove abnormal cells if stress cannot be relieved.	Protect against cell death and keep cells alive.	[19, 22, 23]
Metabolic effects	Does not alter the basic metabolic pathways of the cell.	Glycolysis and lipid synthesis are enhanced to provide energy for rapid proliferation.	[22]
Long-term effects	Maintain tissue homeostasis and remove potentially cancerous cells.	Promote tumor microenvironment remodeling (such as angiogenesis, immunosuppression) and distant metastasis.	[22, 24]

dation [14]. This process modulated by molecular chaperones, folding enzymes and degradation factors associated with the ERQC [14]. However, various physiological and pathological stimuli, such as gene mutations, synthesis errors, cellular microenvironment, molecular crowding, inefficient post-translational mechanisms, Ca^{2+} depletion, nutrient deficiency, oxidative stress and hypoxia, can lead to disorders in the ERQC, resulting in protein misfolding within the ER [14-16]. This phenomenon is referred to as ER stress. The occurrence of ER stress can lead to the compromise of the integrity and functionality of the downstream secretory proteome [14-16]. In response to ER stress, eukaryotes facilitate the proper conformation of proteins through mechanisms of folding, assembly, and disaggregation. Initially, the primary objective of the unfolded protein response (UPR) is to safeguard cellular function by reducing or eliminating unfolded/misfolded proteins and restoring ER homeostasis, the process known as the "Adaptive/Cytoprotective" UPR [17]. However, if these corrective measures are insufficient to restore homeostasis, the UPR may become excessively activated, prompting ER sensors to initiate signals for cellular destruction, the process known as the terminal UPR [18].

Studies have shown that ER stress is activated in a variety of solid tumors. Compared to normal cells, ER stress in cancer cells is different from that in normal cells due to the local microenvironment of the tumor and the high demand for protein synthesis [19-23] (**Table 1**). Emerging evidence suggests that significant ER stress and maladaptive UPR contribute to NSCLC. The UPR is involved in various biological processes in NSCLC that are closely associated with apoptosis [25-27], paraptosis [28, 29], ROS [30], mitochondrial dysfunction [31], drug resistance [32], autophagy [33-36], the cell cycle [37], senescence [38], gluconeogenesis [39] (**Figure 1**). This review synthesizes contemporary research that connects the ER to NSCLC and explores potential pharmacological targets and therapeutic strategies.

The UPR signaling and activation mechanism

The initiation of the UPR signaling pathway is mediated by three ER transmembrane receptors: inositol-requiring enzyme (IRE) 1, protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 α (ATF6α), commonly referred to as UPR sensors. Under resting conditions, the luminal domains of these three ER stress receptors interact with and bind to resident ER-resident chaperone the glucose regulated protein 78 (GRP78)/binding immunoglobulin protein (BiP) to maintain an inactive state [40]. Upon accumulation of unfolded/misfolded proteins, the three receptors dissociate from GRP78. There is also evidence that unfolded proteins bind directly to the luminal domains of IRE1α and PERK [41]. Either mechanism allows for the oligomerization and activation of the sensors and UPR signaling.

IRE1

IRE1, a type I ER transmembrane protein kinase/RNase, represents the most evolution-

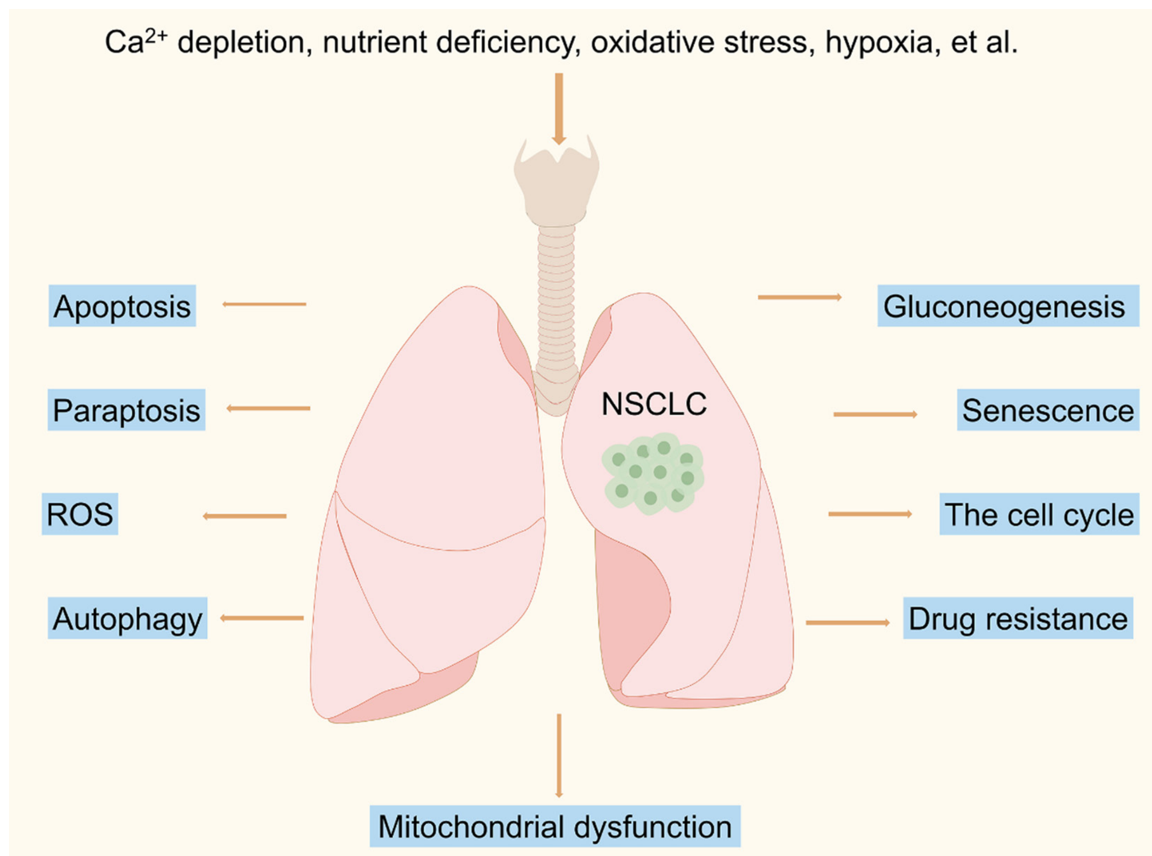

Figure 1. Critical roles of UPR in NSCLC. The UPR is involved in various biological processes in NSCLC. ROS: reactive oxygen species; NSCLC: non-small cell lung cancer; UPR: unfolded protein response.

arily conserved arm of the UPR, present across all eukaryotes from yeast to mammals [42, 43] (**Figure 2**). IRE1 is comprised of four distinct domains: the N-terminal luminal domain (NLD), the linker region, the kinase domain, and the RNase domain, with each domain serving a critical function in the overall activity of the protein. There are two IRE1 genes in the mammalian genome: IRE1α and IREβ. While IRE1α is ubiquitously expressed broadly across various cell types that possess ER, IRE1β expression is restricted to intestinal epithelial cells and lung cells, seemingly playing a specialized role in mucus production [44, 45]. Additionally, IRE1β functions as a dominant-negative suppressor of IRE1α, influencing how barrier epithelial cells manage the response to stress at the host-environment interface [46]. When sufficient protein-folding capability exists within the ER, IRE1α maintains a monomeric state by binding to the molecular chaperone GRP78 through its NLD in the ER lumen, thereby maintaining an inactive state. During ER stress, GRP78 binds to unfolded proteins, thereby releasing IRE1α. Subsequently, NLDs form homodimers and possibly oligomers, and then, IRE1α auto-phosphorylates itself at residue Ser724 via its kinase activity, activating the C-terminal RNase domain and leading to conformational changes [17, 46-48].

Active IRE1α excises a 26-nucleotide intron from the un-spliced mammalian basic region/leucine zipper motif (bZIP) transcription factor X-box binding protein 1 (XBP1) mRNA (in yeast, a 252-nucleotide intron is removed from the HAC1 precursor mRNA), and the RNA ligase RtcB then mediates the ligation of the remaining 5' and 3' fragments and shifts the reading frame to result in translation of a stable and active transcription factor termed spliced XBP1 (XBP1s) [49-51]. XBP1s translocates to the nucleus, upregulates multiple UPR genes encoding ER chaperones and activates UPR elements (UPREs) to reduce the protein load within the ER and restore cellular homeostasis [49].

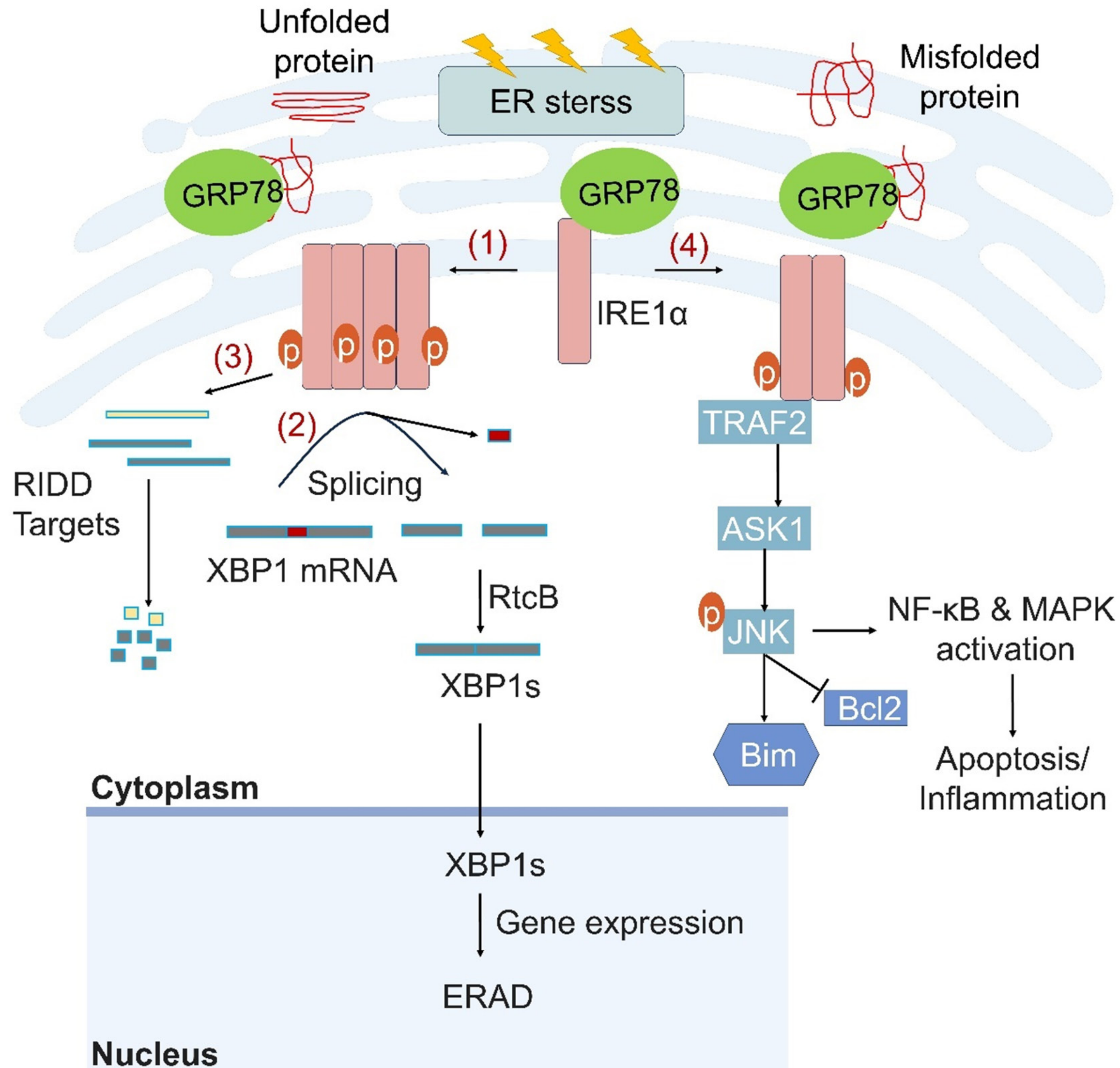

Figure 2. The IRE1α signaling arm of the UPR. In response to ER stress, IRE1α is activated after dissociation from GRP78. Once activated, IRE1 emits signals through three mechanisms. (a) Activated IRE1α RNase splices XBP1 mRNA, which encodes a potent transcription factor XBP1s, which activates the expression of multiple genes involved in the ERAD pathway (1) (2). (b) Active IRE1α can also cleave ER-associated mRNAs or non-coding functional RNAs, leading to their degradation through regulated RIDD, thus reducing the endoplasmic reticulum protein load (1) (3). (c) When activated over time, the cytoplasmic domain of IRE1α also serves as a scaffold to recruit adaptor proteins such as TRAF2, activating the ASK1-JNK signaling cascade, thereby regulating inflammatory or apoptotic responses under atypical ER stress conditions (4). ASK1: apoptosis signal-regulating kinase 1; GRP78: glucose regulated protein 78; ER: endoplasmic reticulum; ERAD: ER-associated degradation; IRE1α: inositol requiring enzyme 1 α; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; RIDD: IRE1-dependent decay; TRAF2: tumor necrosis factor receptor-associated factor 2; UPR: unfolded protein response; XBP1: X-box binding protein 1.

XBP1s regulates the expression of numerous UPR target genes involved in ER folding, glycosylation, and ER-associated degradation (ERAD) [17, 52]. Furthermore, non-XBP1 targets of IRE1 possess properties to maintain homeostasis or induce cell death [53, 54]. Non-XBP1 targets, including mRNA, microRNA, and circRNA, are primarily degraded by IRE1 through the regulated IRE1-dependent decay (RIDD), a novel UPR regulatory pathway that influences cell fate under ER stress and alleviates the need for ER chaperones by reducing the synthesis of secretory proteins [55-58]. A shared characteristic of RNAs regulated by XBP1 and

RIDD is the CUGCAG sequence located within stem-loop structures, which is a key feature of the IRE1α cleavage site [55]. Beyond activating ribonuclease activity, IRE1α can also activate apoptosis signal-regulating kinase 1 (ASK1) by recruiting tumor necrosis factor receptor-associated factor 2 (TRAF2). ASK1 phosphorylates c-Jun N-terminal kinase (JNK), thereby activating the pro-apoptotic protein Bim while inhibiting the anti-apoptotic protein Bcl2 [59-61]. IRE1α/JNK signaling can also activate nuclear factor-κB (NF-κB) and MAPK pathways under ER stress, which can initiate inflammatory or apoptotic responses to varying degrees depending on the specific context [62-65] (**Figure 2**).

In addition, IRE1α signaling is regulated by various factors that influence IRE1α dimerization, oligomerization, phosphorylation, and dephosphorylation. Under conditions of high or chronic ER stress, the tyrosine-protein kinase ABL1 stabilizes IRE1α oligomers, promoting subsequent autophosphorylation of IRE1α, splicing of XBP1 mRNA, RIDD, and cell apoptosis [66]. The pro-apoptotic proteins BAX and BAK form a complex with the cytoplasmic domain of IRE1α, further activating IRE1α and thereby sustaining UPR signaling [67]. BI-1 and Fortilin act as negative regulators of IRE1α. BI-1 forms a complex with the cytoplasmic domain of IRE1α, inhibiting its phosphorylation rate and attenuating IRE1α signaling during ER stress [68]. Fortilin directly interacts with phosphorylated IRE1α, inhibiting both its kinase and RNase activities, thus protecting cells from apoptosis [69]. However, in yeast, the serine/threonine phosphatase Ptc2 was found to negatively regulate IRE1. Ptc2 directly interacts with IRE1 in a Mg^{2+} or Mn^{2+}-dependent manner to dephosphorylate IRE1. Dephosphorylation inactivates IRE1 and prevents HAC1 splicing, thus dampening the UPR [70]. Notably, cell survival ER stress-mediated is unaffected by the loss of Ptc2, indicating that Ptc2 is not essential for cell survival during ER stress, implying that other phosphatases compensate for the loss of Ptc2 or that phosphorylation is not required for IRE1 inactivation.

ATF6

ATF6, a second class of ER stress sensor, is a type II transmembrane protein exclusive to metazoans. It consists of three functional domains: a bZIP transcription factor domain at the N-terminus of the cytoplasmic region, a transmembrane domain, and an ER stress-sensing luminal domain. Mammals express two distinct isoforms of ATF6 proteins: ATF6α and ATF6β, which share a conserved bZIP domain at the N-terminus [71]. In the absence of ER stress, GRP78 binds to the lumenal region of ATF6, anchoring it to the ER via the ER retention sequence at the C-terminus of GRP78, thereby keeping ATF6 inactive [72, 73]. Under ER stress conditions, ATF6α is the predominant isoform responsible for regulating the expression of ER stress-response genes. In response to ER stress, the association between GRP78 and ATF6α is disrupted, which causing ATF6α to expose two Golgi-localization signals (GLS1 and GLS2). Then this signal initiates the translocation of ATF6α to the Golgi apparatus where it undergoes proteolytic cleavage by two resident proteases [72]. Site 1 protease (S1P) and Site-2 protease (S2P) sequentially remove the lumenal domain and transmembrane anchor of ATF6α. This cleavage releases the N-terminal 50-kDa cytosolic portion of ATF6, which has a nuclear localization sequence and promotes its movement to the nucleus, where it acts as a transcription factor to activate ER stress target genes [72, 73]. The transcriptional upregulation of XBP1 mRNA, which is non-canonically spliced by IRE1α, is also mediated by activated ATF6, thereby allowing the translation and activation of XBP1 [49, 74] (**Figure 3**).

While ATF6α and ATF6β share structural similarities, the role of ATF6β remains less clear compared to that of ATF6α. Previous studies have suggested that ATF6β may function as an endogenous repressor of ATF6α, finetuning the intensity and duration of ATF6α signaling during ER stress [73, 75]. Furthermore, ATF6β has been found to play a role in ER stress through Ca^{2+}. Calreticulin, a molecular chaperone with a high Ca^{2+} binding capacity in the ER is specifically regulated by ATF6β [76]. Deficiency of ATF6β reduces Ca^{2+} storage in the ER and enhances ER stress-induced cell death [76]. However, a recent in vitro study has further demonstrated the activation of ATF6β under ER stress conditions [77]. In fact, another study corroborated this finding. During ER stress, ATF6β dissociates from GRP78 and is cleaved by the proteases S1P and S2P. The

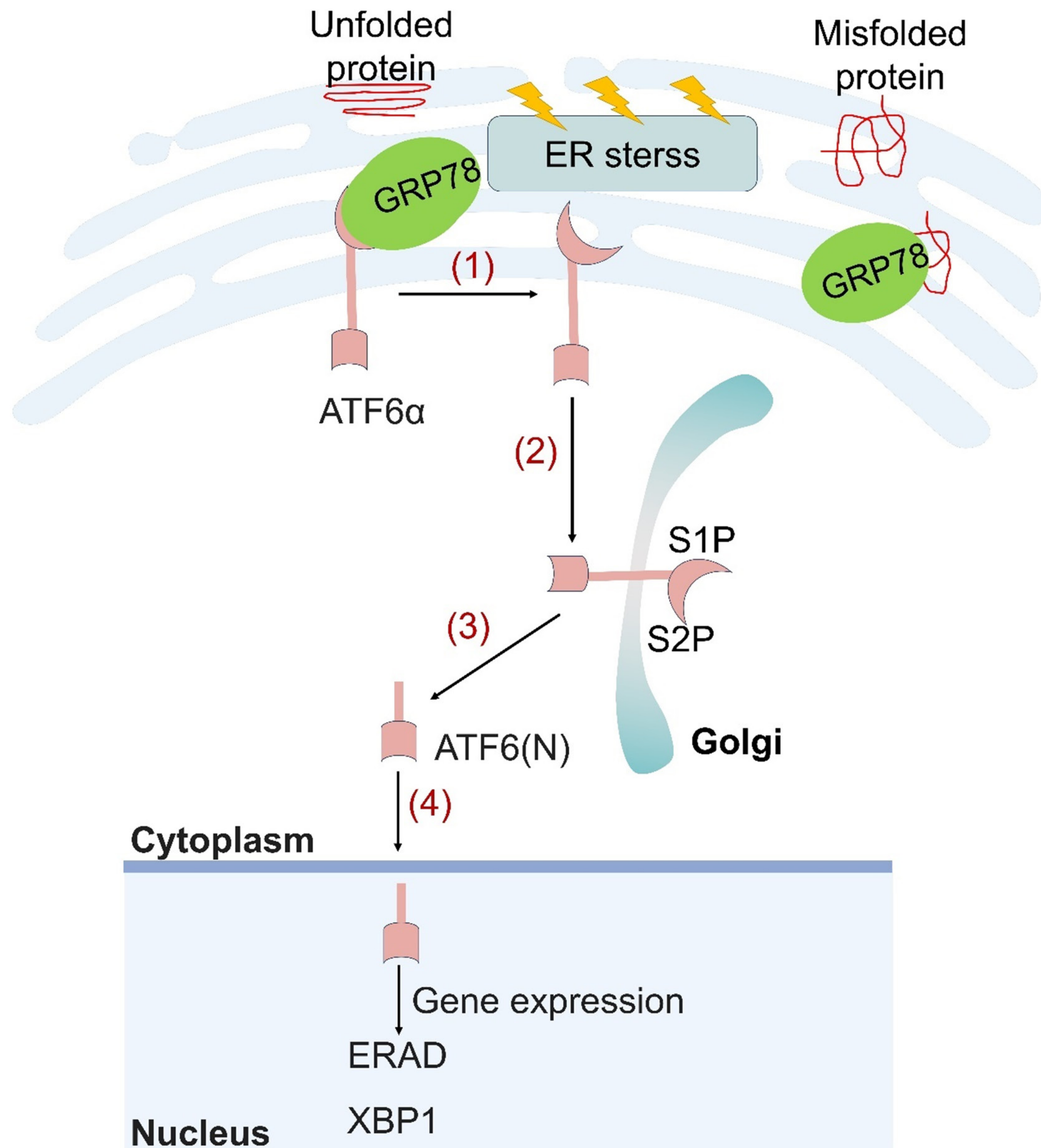

Figure 3. The ATF6 signaling arm of the UPR. Upon ER stress, GRP78 dissociates from the ER intraluminal domain of ATF6α, which allows the 90 kD form of ATF6α to translocate to the Golgi apparatus (1) (2). It is cleaved by S1P and S2P, releasing the N-terminal approximately 400 amino acids (50 kD) of ATF6α (3). Activated ATF6 translocates to the nucleus, inducing transcription and expression of ERAD-related genes (4). ATF6: activating transcription factor 6; GRP78: glucose regulated protein 78; ER: endoplasmic reticulum; ERAD: ER-associated degradation; S1P: Site-1 protease; S2P: Site-2 protease; XBP1: X-box binding protein 1.

active fragment of cleaved ATF6β translocates to the nucleus, enhancing the expression of the C/EBP homologous protein (CHOP) and cleaved caspase-3, thereby promoting apoptosis [78]. Therefore, the distinct roles of ATF6α and ATF6β under ER stress conditions warrant further investigation.

PERK

PERK is a type I ER transmembrane protein exclusive to metazoans. It consists of a luminal ER stress-sensing domain and a cytoplasmic kinase domain. Similar to IRE1, PERK is maintained in an inactive conformation by the bind-

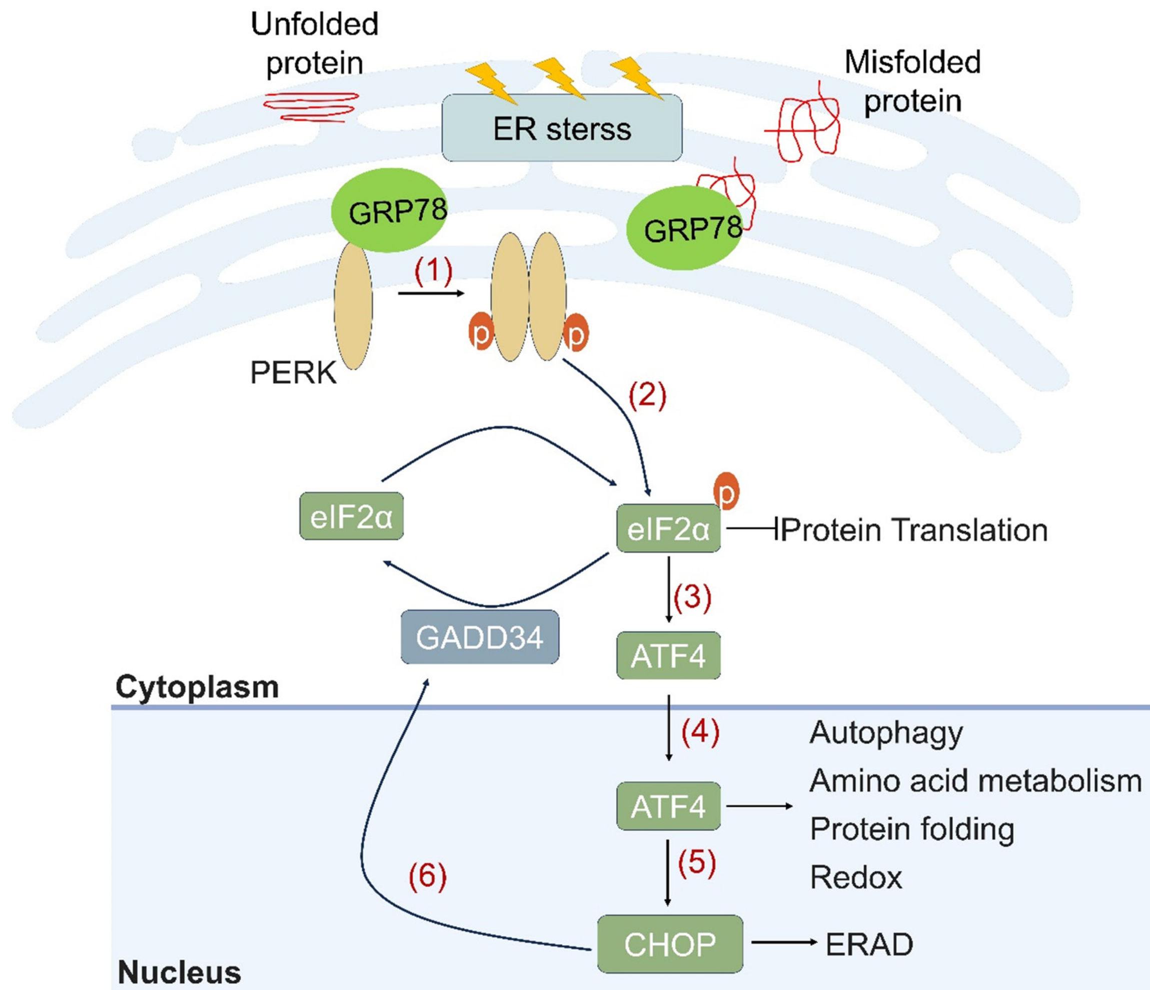

Figure 4. The PERK signaling arm of the UPR. The presence of misfolded proteins leads to the dissociation of GRP78 from PERK, resulting in PERK activation (1). PERK phosphorylates eIF2α to attenuate protein translation (2). Given that PERK activation is sustained, ATF4 is upregulated by phosphorylated eIF2α, which then promotes transcription of target genes involved in autophagy, amino acid metabolism, protein folding and redox homeostasis (3) (4). Under long-term ER stress, the pro-apoptotic protein CHOP is activated (5). As a result, CHOP upregulates GADD34, which in turn dephosphorylates eIF2α (6). ATF4: activating transcription factor 4; GRP78: glucose regulated protein 78; ER: endoplasmic reticulum; ERAD: ER-associated degradation; PERK: protein kinase RNA-like ER kinase; eIF2α: eukaryotic initiation factor 2 alpha; CHOP: C/EBP Homologous Protein; GADD34: growth arrest and DNA damage-inducible 34.

ing of GRP78 to its luminal domain [79]. PERK initiates immediate adaptive responses to ER stress.

In response to ER stress, GRP78 dissociates from the luminal region of PERK, triggering its oligomerization and autophosphorylation. The luminal domain of PERK oligomerizes to form stable dimers, which subsequently undergo a helix swap or intertwining of two dimers via helical subunits, leading to a transient tetrameric state [80]. This tetrameric state facilitates enhanced phosphorylation efficiency [80]. Activated PERK, through its cytoplasmic domain (which possesses Ser/Thr kinase activity), phosphorylates serine 51 of the eukaryotic initiation factor 2α (eIF2α). Phosphorylated eIF2α inhibits the GTP-exchange activity of the initiation factor eIF2B, leading to a significant reduction in cap-dependent translation initiation in response to ER stress, ultimately decreasing the load on the ER [81] (**Figure 4**).

On the other hand, phosphorylated eIF2α initiates the translation of activating transcription factor 4 (ATF4), a member of the basic leucine

zipper protein family. mRNA of ATF4contains an overlapping upstream open reading frame in its 5' untranslated region, which is required or preferential for ATF4 translation when eIF2α is phosphorylated [81]. ATF4 is a stress-inducible transcription factor that promotes cell survival and enhances resistance to oxidative stress by inducing genes involved in amino acid metabolism, redox reactions, and protein secretion [82]. Additionally, ATF4 induces autophagy-related genes that are crucial for autophagosome formation and function [83]. However, not all genes induced by ATF4are anti-apoptotic. It is well known that the induction of the transcription factor CHOP is strongly dependent on ATF4, leading to the expression of multiple pro-apoptotic molecules that promote apoptosis [84]. The apoptosis-related targets of CHOP are as follows: (a) Tribbles homolog 3 (TRB3), identified as a novel ER stress-induced gene that involved in autophagic cell death by inducing ER stress and activating the UPR [85]; (b) Death receptor 5 (DR5), a caspase-activated cell surface death receptor belonging to the tumor necrosis factor receptor family [86]; (c) Ero1α (ER oxidoreductase-1), which causes ER hyperoxidation and promotes cell death [87]; and (d) Growth arrest and DNA damage-inducible 34 (GADD34), a phosphatase regulatory subunit that dephosphorylates eIF2α to restore protein translation following ER damage [88]. Another potential mechanism by which CHOP induces apoptosis is through the direct inhibition of Bcl-2 transcription and the induction of Bim expression [89]. Activating transcription factor 3 (ATF3) is also a critical molecule induced by ATF4, participating in the feedback control of the eIF2 kinase stress response by binding to the promoter region of GADD34 [90] (**Figure 4**).

The PERK signaling pathway is crucial for maintaining mitochondrial structural and functional integrity, calcium dynamics, and metabolic regulation. As a key component of the mitochondria-associated ER membrane (MAM), PERK facilitates physical and functional connections between the ER and mitochondria. Under conditions of ER stress, thePERK-ATF4-CHOP pathway mediates mitochondrial apoptosis by upregulating BH3 proteins. Conversely, during reactive oxygen species (ROS)-induced oxidative stress, the reduction of mitochondrial fusion protein 2 (Mfn2) can activate PERK, leading to a decrease in MAM, which triggers mitochondrial dysfunction and subsequent cell apoptosis [91, 92]. Moreover, the PERK-ATF4 signal can induce the expression of Parkin, a protein that mediates mitophagy, promoting cell survival by maintaining mitochondrial homeostasis [93]. Furthermore, the PERK-dependent eIF2α phosphorylation-induced translational attenuation mechanism can promote protective stress-induced mitochondrial hyperfusion (SIMH), which can prevent pathological mitochondrial fragmentation and promote mitochondrial metabolism in response to ER stress, but this process is independent of the transcriptional activity of ATF4 [94]. In addition to eIF2α, the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) is also a direct substrate of PERK. PERK phosphorylates threonine 80 of NRF2 for activation, a process that does not require the accumulation of ROS. Phosphorylated NRF2 dissociates from Kelch-like ECH-associated protein 1 (Keap1), translocates to the nucleus, and activates the expression of its target genes to facilitate cellular redox regulation during ER stress [95].

Summary of components engaged in ER stress signaling in NSCLC

ER-resident components engaged in NSCLC

The ER is enriched with various molecular chaperones that ensure the proper folding of newly synthesized proteins. The expression of GRP78, a major ER chaperone, is closely associated with the differentiation and development of NSCLC, with elevated levels predicting poor prognosis in patients [96]. Increased GRP78 has also been shown to promote epithelial-to-mesenchymal transition (EMT) in A549 under hypoxic conditions [97]. In addition, GRP78 expression is elevated in epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)-resistant NSCLC, and the inhibition of GRP78 can enhance ER stress and the subsequent generation of reactive oxygen species (ROS), leading to growth suppression [98]. Ribosome-binding protein 1 (RRBP1), an ER membrane-bound protein, exhibits elevated expression in human NSCLC tissues, correlating positively with adverse patient prognosis [25, 99].

The role of UPR signaling in NSCLC has been well established. For instance, icariin II can activate ER stress, including the three branches of UPR signaling: PERK, IRE1, and ATF6. This

activation also involves the downstream of PERK-eIF2α-ATF4-CHOP pathway, which enhances cisplatin-induced apoptosis in NSCLC cells [26]. Butein mediates apoptosis in NSCLC cells through the generation of ROS and apoptotic pathways that depend on the PERK/eIF2α/CHOP signaling cascade. Notably, the inhibition of ER or oxidative stress can partially eliminate the tumor growth-inhibitory effects induced by Butein [100]. In addition, XBP1s has also been reported to be overexpressed in patients with lung adenocarcinoma (LUAD), indicating a poor prognosis in patients [101], and the splicing of XBP1 is a valuable biomarker of NSCLC invasiveness, and this process is closely related to RE1α endoribonuclease activity [102]. Another study also finds that overexpressed XBP1s protein correlates with the Tumor-Node-Metastasis (TNM) stage, lymph node metastasis and poor prognosis of NSCLC [103, 104]. XBP1s protein can upregulate the expression of insulin-like growth factor binding protein 3 (IGFBP3) and regulate the invasion and metastasis of NSCLC cells by regulating IGFBP3 [103]. Thus, XBP1s not only serves as a potential biomarker for metastasis and prognosis but also represents a promising therapeutic target for NSCLC. In addition, increased expression of PERK downstream targets has been observed in various subtypes of NSCLC and is associated with a more aggressive phenotype, high risk of recurrence, and poor prognosis [105, 106], suggesting involvement of the PERK pathway in NSCLC development. Although many PERK inhibitors have been studied as potential anticancer drugs, there are few reports on their applicability in the treatment of NSCLC [107, 108]. Recently, it's found that treatment with the selective PERK inhibitor NCI 159456 significantly reduced apoptosis and increased DNA damage levels in normal and ER-stressed NSCLC cells [109]. Importantly, this inhibitor does not exert any detrimental effects on normal human lung cells [109]. The results of this investigation endorse the prospective utilization of PERK inhibitors in the targeted treatment of NSCLC. In brief, precise analysis of ER stress in NSCLC may uncover new therapeutic strategies.

Molecules engaged in ER stress signaling in NSCLC

In addition to the ER-resident components engaged in NSCLC, multiple molecules have been shown to engaged in NSCLC through ER signaling. Inactivating mutations of liver kinase B1 (LKB1) occur with a high frequency in subtypes of NSCLC [110, 111]. Loss of LKB1 in NSCLC cells increases sensitivity to pharmacological compounds that exacerbate ER stress [110]. Ficolin 3 (FCN3) functions as a tumor suppressor in LUAD. Studies have shown that downregulation of FCN3 is significantly correlated with increased mortality in LUAD patients. FCN3 contributes to LUAD by inducing ER stress [112]. The knockdown of tissue transglutaminase 2 (TG2) triggers ER stress and disrupts redox homeostasis, activating both intrinsic and extrinsic apoptotic pathways, which ultimately leads to NSCLC cell death [113]. In A549 NSCLC cells, the interaction between the TOR signaling pathway regulator-like (TIPRL) protein and eIF2α results in the phosphorylation of eIF2α and activation of the eIF2α-ATF4 pathway. This activation enhances the ability of cancer cells to withstand metabolic stress and may facilitate the development of malignant tumors through autophagy [114]. Conversely, the ablation of TIPRL significantly reduces autophagy induction, leading to decreased cancer cell survival and increased cell death [114]. Therefore, targeting genetically induced metabolic and ER stress may become a novel therapeutic approach for treating various types of cancer. As an important regulatory subunit of protein phosphatase 4 (PP4), high expression levels of protein phosphatase 4 regulatory subunit 1 (PP4R1) are associated with poor prognosis of NSCLC and are closely related to the TNM stage and clinical stage of NSCLC patients [115]. PP4R1 promotes malignant progression in NSCLC by upregulating HSPA6 expression, further activating ER stress [115]. P21-activated kinase (PAK), a member of the serine/threonine protein kinases family, exhibits mutationally activated or overexpressed PAK isoforms in numerous human solid malignancies. Elevated levels of P21-activated kinase 4 (PAK4) have been previously associated with poor prognosis in NSCLC and promote migration and invasion [116].

Meanwhile, several molecules have been identified as contributors to chemoresistance in NSCLC via ER signaling pathways. For example, enhanced expression of PAK4 has recently been observed in both cisplatin-resistant NSCLC tumors and cell lines [116]. Inhibiting of PAK4 has demonstrated the potential to sensi-

Table 2. Components in ER stress signaling engaged in NSCLC

Molecule	Expression	Effects	Reference
FCN3	Down-regulated in LUAD tissues (*vs*. normal tissues)	Ectopic expression of FCN3 led to cell cycle arrest and apoptosis in A549 and H23 cells derived from LUAD	[112]
GRP78	Up-regulated in NSCLC tissues (*vs*. normal tissues)	Closely related to tumor stage and worse patient survival	[96]
GRP78	GRP78 expression in A549 cells increased significantly under hypoxic conditions	GRP78 promotes EMT by activating Smad2/3 and Src/MAPK pathways	[97]
GRP78	Up-regulated in EGFR-TKI-resistant NSCLC cells (*vs*. gefitinib-sensitive control)	Associated with tumor growth	[98]
LKB1	Inactivating mutations occur at a high frequency in NSCLC subtypes	Associated with URP-mediated apoptosis	[110]
PAK4	Up-regulated in NSCLC tissues (*vs*. normal tissues)	Associated with invasion and migration progression of NSCLC	[116]
PERK	Activation in NSCLC tissue and A549	contribute to the development and progression of NSCLC	[109]
PP4R1	Highly expressed in NSCLC cell lines H1299 and HCC827	After overexpression of PP4R1 in *vitro*, cell proliferation, colony growth, migration and invasion abilities were significantly enhanced	[115]
RRBP1	Increased expression in NSCLC cell lines A549, PC9, and H1299	Positively correlated with shorter overall survival in LUAD patients	[25]
SCD1	Up-regulated in LUAD tissues (*vs*. normal tissues)	Associated with poor prognosis in patients with early LUAD	[121]
TIPRL	High levels in LUAD tissue and A549	Positively correlated with tumor malignancy and contribute to cell survival	[114]
TG2	Higher level in A549	TG2 promotes proliferation through AKT activation	[113]
XBP1s	Up-regulated in LUAD tissues (*vs*. normal tissues)	Closely related to patient survival	[101]
XBP1s	Up-regulated in NSCLC tissues (*vs*. normal tissues)	Correlation with NSCLC TNM stage, lymph node metastasis, and poor prognosis	[103]

tize resistant tumor cells by modulating ER stress [116]. Numerous studies indicate that cancer stem cells play a significant role in chemotherapy resistance [117, 118]. The enzyme stearoyl-CoA desaturase 1 (SCD1) has been linked to poor prognosis and lower survival rates in LUAD, regulating the survival and proliferation of LUAD stem cells through YAP/TAZ activation [119, 120]. Notably, blocking SCD1 with the SCD1 inhibitor MF-438 can induce ER stress responses and enhance autophagy, thereby inhibiting the formation of three-dimensional (3D) LUAD spheroids and reversing cisplatin resistance [121]. Therefore, targeting ER stress response mechanisms may provide a promising strategy to combat chemoresistance in NSCLC.

Therefore, targeting UPR components or factors associated with ER stress signaling holds promise as a therapeutic strategy against ER stress-related pathologies, presenting novel avenues for the treatment of NSCLC. All the above factors that mediate NSCLC through ER stress signaling are summarized in **Table 2**.

Investigations into drugs aiming at ER homeostasis in NSCLC

In recent years, with growing recognition of chronic ER stress in cancer cells and the critical roles of associated UPR in the progression of NSCLC, modulation of UPR signaling components has emerged as a means to either stimulate or attenuate protein folding, thereby facilitating anticancer strategies. To date, however, the mechanisms defining the thresholds at which UPR signaling transitions from adaptive cell protection to pro-apoptotic cell death, or vice versa, remain to be elucidated. Activation of ER stress is closely related to signaling pathways such as autophagy [33-35], oxidative stress [31], apoptosis [25-27], Ca^{2+} homeostasis [36, 122], metabolic disorders [39, 123], and inflammatory response [124]. As a result, there is burgeoning interest in exploring UPR as

a potential therapeutic target. Next, we will review drugs targeting ER stress signaling in NSCLC.

ER stress-mediated autophagy induced by drugs

When developing new drugs for the treatment of NSCLC, researchers discovered that certain drugs can trigger ER stress-mediated autophagy. Autophagy can exert either tumor-suppressive or tumor-promoting functions depending on the stage and environment of tumor development [125, 126]. This suggests that these drugs may exert anti-tumor or protective effects through ER stress-mediated autophagy. For instance, crassolide activates the ER stress pathway through ROS accumulation, leading to increased autophagosome formation and resulting in achieving anti-tumor effects [127]. Of course, other molecules have also played a role in cytotoxic autophagy in the treatment of NSCLC, such as the antidepressant fluoxetine, the anticancer drug ABTL0812 (autophagy inducer), and total ginsenosides [33, 35, 128]. Conversely, in A549 cells treated with rafoxanide, the compound significantly induced apoptosis via ER activation, while autophagy is activated to prevent ER-induced cell apoptosis [129]. Similarly, H1, a bromized derivative of tetrandrine, induces ER stress-mediated expression of eDR5 and apoptosis in NSCLC cells. H1-induced autophagy plays a protective role in NSCLC cells and effectively attenuates caspase-mediated cell apoptosis [130]. Cytoprotective autophagy has also been observed when other molecules (salinomycin, cucurbitacin E, the natural product toosendanin, and glycyrrhetinic acid) are utilized in the treatment of NSCLC [34, 131-133]. These results indicate that ER stress-mediated autophagy plays a significant role in maintaining the survival of NSCLC cells within the challenging tumor microenvironment. However, the anti-apoptotic or pro-apoptotic effects of autophagy are influenced by various molecules, and the underlying mechanisms remain unclear, warranting further investigation. Additionally, these studies suggest a need for therapeutic strategies that target ER stress signals or autophagy in cancer treatment.

Drugs inducing ER stress-mediated cell death

ER stress, as a crucial biological response following drugs treatment, has been proven to trigger a variety of cell death mechanisms, including caspase-dependent [27] or caspase-independent apoptosis [134], as well as non-apoptotic cell death modes such as paraptosis [135], ferroptosis [136], and immunogenic cell death (ICD) [137, 138], profoundly impacting the fate of tumor cells.

ER stress-mediated apoptosis: Multiple cellular stimuli may impair protein homeostasis in the ER, and activate the UPR to cope with this state. However, if the UPR fails to restore homeostasis and ER stress is not alleviated, cell death signals will be activated, leading to cell apoptosis. A variety of cellular stimuli may impair protein homeostasis in the ER and activate the UPR to cope with this state. However, if the UPR of the ER cannot reestablish homeostasis and ER stress cannot be relieved, cell death signals will be activated, leading to cell apoptosis. The combination treatment of Icariside II and cisplatin induces cell death by activating three major sensors of the ER stress response (PERK, IRE1, and ATF6), as well as promoting caspase-dependent apoptosis in NSCLC cell lines [26]. Ciclopirox induces PERK-dependent ER stress by impairing mitochondrial function and enhancing ROS generation in NSCLC cells, activating a caspase-dependent apoptotic pathway leading to NSCLC cell apoptosis [27]. Regorafenib enhances the expression of NADPH oxidase 5 (NOX5), which increases ROS production, activates ER stress and induces caspase-dependent cell apoptosis [30]. Curcumol directly inhibits the enzyme activity of NRH: quinone oxidoreductase 2 (NQO2), leading to ROS generation and ER stress, which triggers caspase-dependent cell apoptosis in a CHOP-dependent manner [139]. Moreover, caspase-independent pathways also contribute to cell apoptosis. It has been reported that (Z)3,4,5,4'-trans-tetramethoxystilbene (TMS), a novel analogue of resveratrol, significantly induces ER stress and leads to caspase-independent cell apoptosis in gefitinb-resistant NSCLC cells by elevating the intracellular Ca^{2+} levels [134].

Although pharmaceutical treatment can lead to either caspase-dependent or caspase-independent apoptosis due to ER stress, it remains unclear under which specific circumstances the ER selects one pathway over the other.

ER stress-mediated paraapoptosis: In addition to caspase-dependent and caspase-indepen-

dent apoptosis triggered by ER stress, certain drugs can induce alternative forms of cell death. Paraapoptosis is a caspase-independent form of programmed cell death that lacks typical morphological changes associated with apoptosis and is characterized by swelling of the ER and/or mitochondrial and cytoplasmic vacuolation [140]. Recent studies have demonstrated that ER stress-mediated paraapoptosis plays an important role in the antitumor effects of various drugs [141, 142]. For instance, it has been reported that chalcomoracin and epimedokoreanin B both induce paraapoptotic-like cell death by activating ER stress [28, 135]. Additionally, another study found that the combination of afatinib and celastrol activated ER stress through ROS accumulation and mitochondrial Ca^{2+} overload, thereby inducing paraapoptotic-like cell death in NSCLC cells [143]. This type of paraapoptotic cell death suggests that traditional methods for detecting apoptosis may be insufficient to fully evaluate the anticancer efficacy of drugs. From a clinical perspective, a deeper understanding of the mechanisms underlying drug-induced paraapoptotic-like cell death can inform rational drug use and help mitigate unnecessary toxic side effects.

ER stress-mediated ICD: ICD is also a form of programmed cell death that can activate adaptive immune responses in immunocompetent hosts [144]. It is characterized by the pre-apoptotic translocation of calreticulin (CRT) from the ER to the cell surface, which occurs as a result of an ER stress response accompanied by the phosphorylation of eIF2α. Research has been shown that CRT is overexpressed at both the cytoplasmic and cellular membrane levels in NSCLC cells [141], suggesting a potential association between NSCLC and ICD. Furthermore, Jitka et al. find that in certain subgroups of NSCLC, the ER stress response leads to CRT expression and exposure, which in turn triggers the activation of adaptive immune responses within the tumor microenvironment, thereby facilitating anticancer immune surveillance [145]. It is understood that ICD is the most relevant type of cell death under ER stress, as the ER plays a central role in nearly all instances of ICD [146, 147]. For example, marsdenia tenacissima extract (MTE) induced ICD in NSCLC cells by inhibiting AXL phosphorylation [137]. When ER stress inhibitors are added to MTE-treated cells, changes are observed in the activity of ICD hallmark molecules, specifically adenosine-5'-triphosphate (ATP) and high mobility group box 1 (HMGB1), indicating that MTE triggers ER stress-related ICD [137]. Additionally, afzelin can inhibit the progression of NSCLC by inducing ICD [148]. Afzelin activates ER stress and induces ICD by targeting NQO2 (a flavin adenine mononucleotide-dependent quinone oxidoreductase), which inhibits cell viability and proliferation in A549 and H1299 cells, leading to an increased rate of apoptosis [148]. The Iridium (III) complex (Ir1), which contains an N, N-bis (2-chloroethyl)-azane derivate, can act as an ER-targeted ICD inducer in NSCLC, and produce long-lasting antitumor immunity by activating ICD in A549 cells [149].

However, these ICD inducers are currently in the preclinical research stage, and their safety has yet to be thoroughly evaluated. Therefore, there is still a considerable distance to cover before ER stress-related ICD research progresses to clinical trials.

ER stress-mediated ferroptosis: The characteristic of ferroptosis is that under the action of ferrous iron or lipoxygenase, it catalyzes the lipid peroxidation in unsaturated fatty acids that are abundantly expressed on the cell membrane, facilitated by ferrous iron or lipoxygenase. This process is regulated by the antioxidant system, which modulates the activity of the core enzyme glutathione peroxidase 4 (GPX4), ultimately leading to cell death [150, 151]. There is growing evidence that ER stress-mediated ferroptosis can inhibit tumor initiation and progression in both tumor and immune cells. However, the research on ER stress-mediated ferroptosis in NSCLC remains limited. Currently, only fascaplysin has been identified as a compound that activates the ER stress response via SLC7A1, inducing iron-dependent cell death in A549 cells [136]. Although ER stress-mediated ferroptosis has been identified in NSCLC, the underlying mechanisms still require thorough investigation. The discovery of ferroptosis, particularly its intrinsic connection to ER stress, may pave the way for future research and potentially serve as a novel therapeutic target for NSCLC.

Several drugs that target ER stress signaling for the potential therapy of NSCLC, described above or in previous studied, are summarized in **Table 3**.

Table 3. Drugs aiming at ER homeostasis in NSCLC

Drug	UPR mediator	In *vitro* or *vivo* model	Mechanisms of action and effects	Clinical applications	Reference
ABTL0812	ATF4	A549	ABTL0812 increases the levels of cellular long-chain dihydroceramides by impairing DEGS1 activity, which resulted in sustained ER stress and activated UPR via ATF4-DDIT3-TRIB3 that ultimately promotes cytotoxic autophagy and cell death in cancer cells.	ABTL0812 in combination with paclitaxel/carboplatin was studied in a phase II study in patients with squamous NSCLC.	[33, 152]
Ciclopirox	PERK, eIF2α, ATF4 and CHOP	H1299 and 95D	Ciclopirox impairs mitochondrial function and enhances the production of ROS in cells Enhanced ROS activates UPR in the ER via PERK-eIF2α-ATF4-CHOP to drive Caspase-3-dependent apoptosis, ultimately inhibiting NSCLC cell migration and invasion.	Ciclopiroxx is mainly used in clinical practice to treat fungal infections.	[27]
Crassolide	PERK	H460	Crassolide activates the ER stress pathway by increasing the protein levels of p-eIF2α and CHOP via ROS, thereby inducing autophagy-mediated cell death and G2/M blockade in NSCLC cells.	In the stage of cell experiments.	[127]
Curcumol	CHOP	A549 and H1299, xenograft models	Curcumol directly targets NQO2 to cause ROS generation, which activates ER Stress-CHOP signaling to upregulate DR5, sensitizing NSCLC cell to TRAIL-induced apoptosis, thus achieving synergistic killing effect with TRAIL on cancer cells.	It has progressed to animal experiments.	[139]
Fluoxetine	PERK, ATF4 and CHOP	H460 and A549	Triggering the ATF4-AKT-mTOR signaling pathway, inducing cell cycle arrest and autophagy, and inhibiting the growth of cancer cells.	Fluoxetine is one of the latest clinical anti-depressants. Fluoxetine is still in the cell experiments for NSCLC treatment.	[128]
H1	GRP7, IRE1α, p-eIF2α and CHOP	A549, Calu-1 and H157	H1 induces DR5 dependent cell apoptosis by enhancing the ER stress signaling pathway, while triggering protective autophagy, effectively reducing caspase mediated cell apoptosis.	In the stage of cell experiments.	[130]
Icariside II	PERK, IRE1 and ATF6	Lewis lung carcinoma (LLC) cells, H1299 and A549, xenograft models	Icariside II enhances cisplatin-induced apoptosis by activating ER stress, including three branches of UPR signaling, PERK, IRE1, and ATF6, and the downstream PERK-eIF2α-ATF4-CHOP pathway.	It has progressed to animal experiments.	[26]
Rafoxanide	PERK, IRE1 and ATF6	A549 and H1299, xenograft models	Rafoxanide induces ERs and activates all three UPR pathways in cells, thereby inducing apoptosis and cell cycle arrest. At the same time, autophagy was activated to partially alleviate ER stress.	Rafoxanide is an antihelminthic drug that is used to combat fluke infections in ruminant. Rafoxanide has progressed to animal experiments for NSCLC treatment.	[129]
Regorafenib	ATF4, p-eIF2α	H1299 and PC-9, xenograft models	Significantly enhancing cisplatin-induced lung cancer cytotoxicity by activating ROS-mediated ER Stress, c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) signaling pathways.	Regorafenib in combination with toripalimab for colorectal cancer has been studied in phase Ib/II. Regorafenib in the treatment of NSCLC has been performed in a mouse xenograft model.	[30, 153]

Salinomycin	ATF4 and CHOP	A549, Calu-1 and H157	Salinomycin stimulates ER stress and mediates autophagy via the ATF4-DDIT3/CHOP-TRIB3-AKT1-MTOR axis. While ER stress-mediated autophagy protects cells from salinomycin-induced apoptosis.	In the stage of cell experiments.	[34]
TMS	PERK, p-eIF2α	H1975	TMS increases intracellular [Ca^{2+}] levels by directly binding to SERCA, leading to ER stress and AMPK activation, inducing caspase independent apoptosis and autophagy.	In the stage of cell experiments.	[134]
Toosendanin	ATF6, IRE1, GPR78 and CHOP	A549, xenograft models	Aggravating Ca^{2+} overload, ER stress thus ultimately triggering apoptosis; Inducing autophagy, recruiting membrane DR5, and subsequently antagonizing apoptosis sensitivity.	Toosendaninhas progressed to animal experiments for NSCLC treatment.	[133]
Total ginsenosides	ATF4 and CHOP	A549 and PC-9	Inducing autophagic cell death by mediating autophagy through the ATF4-CHOP-AKT1-mTOR axis.	Total ginsenosides are in clinical trials for bone metabolism and in cellular trials for the treatment of NSCLC.	[35, 154]
Afatinib and celastrol	ATF6, IRE1 and CHOP	H23 and H292, xenograft models	Inducing paraptosis by activating ER stress via intracellular ROS accumulation and mitochondrial Ca^{2+} overload.	Progressed to animal experiments for NSCLC treatment.	[143]
Chalcomoracin	GPR78 and CHOP	H460, xenograft models	Inducing paraapoptotic-like cell death and inhibiting cell proliferation via ER stress and activation of MAPK pathway.	Progressed to animal experiments for NSCLC treatment.	[28]
Epimedokoreanin B	PERK, ATF6 and IRE1α	A549 and NCI-H292, xenograft models	Epimedokoreanin B induces cell death through inducing ER-related paraptosis accompanied by autophagosome accumulation. During this process, all three UPR pathways are activated.	Progressed to animal experiments for NSCLC treatment.	[135]
Afzelin	PERK, eIF2α, GRP78 and CHOP	A549 and H1299	Afzelin inhibits lung cancer progression by activating ER stress through upregulation of p-PERK and p-eIF2α levels via NQO2, which increases the levels of ATP, HMGB1, and CRT, leading to ICD in cells.	In the stage of cell experiments.	[148]
MTE	ATF6, GRP-78, ATF4, XBP1s and CHOP	PC-9 and H1975	MTE reduces mitochondrial membrane potential and increased ROS production. At the same time, ER stress-related proteins and ICD related markers (ATP, HMGB1) are upregulated, thereby inhibiting tumor progression.	In the stage of cell experiments.	[137]
Fascaplysin	ATF4	A549, xenograft models	Fascaplysin induces apoptosis by promoting elevated ROS and induces iron death by regulating the GPX4 signaling pathway via ER stress.	Progressed to animal experiments for NSCLC treatment.	[136]

DEGS1: delta 4-desaturase, sphingolipid 1; DDIT3: DNA damage inducible transcript 3; TRIB3: tribbles pseudokinase 3.

Currently, therapeutic strategies for ER stress have gradually become a research hotspot, but the potential toxicity and drawbacks of these drugs still need to be thoroughly explored. Most of the drugs in **Table 3** are currently in the in vitro phase or in animal studies, and only ABTL0812, Regorafenib, and Total ginsenosidesi have been tested and studied in clinical trials, but only ABTL0812 was used in a phase II study in patients with squamous NSCLC [152-154]. From these conducted clinical studies, it is reasonable to speculate that these drugs also have side effects in clinical applications, for example, gastrointestinal toxicity: decreased appetite, weakness, diarrhea, nausea, and vomiting [152-155]; hepatotoxicity: abnormalities of hepatic function, elevated aminotransferases and bilirubin [153]; immune-related toxicity: may cause immune pneumonia or skin toxicity, such as rash [153, 154]; cardiotoxicity: patients may develop cardiac arrhythmias [153]; hematologic adverse events: neutropenia, anemia, and thrombocytopenia [152, 153]. Of course, there are other adverse effects, such as alopecia, sudden death, infectious shock, neurotoxicity, cough, dysgeusia, headache, myalgia, abdominal pain and hyperthyroidism. Due to genetic polymorphisms and tumor heterogeneity, the response to ER stress therapy varies significantly among patients [152]. In addition, activation of GPR78 may lead to drug resistance in tumor cells through activation of bypass signaling pathways [156]. Therefore, although targeting ER stress therapy provides a new therapeutic direction for NSCLC, its toxicity and drawbacks cannot be ignored.

Conclusion and future outlook

The core role of ER stress in the development of NSCLC has been identified, and there are still many new questions to be addressed. However, it is now clear that ER stress integrates many anti-tumor and tumor-suppressing genes involved in the development of NSCLC. Given the multiple roles of ER stress in the treatment of NSCLC, the following suggestions are intended to guide the future direction of drug development: (a) Exploration of combination therapy: Since a single apoptotic pathway often fails to address the needs of all patients, the combined use of drugs that can induce apoptosis, ferroptosis, and ICD may significantly improve the treatment effect and reduce the emergence of drug resistance. (b) Personalized treatment approaches: Gaining deeper insights into the specific manifestations of ER stress within each NSCLC patient allows for tailored treatment plans that increase specificity while decreasing the likelihood of adverse reactions. (c) Discovery of biomarkers: Actively looking for biomarkers related to ER stress to predict drug responsiveness and disease prognosis, which is helpful for early diagnosis and timely adjustment of treatment strategies. (d) Deepening basic research: Intensifying scientific investigation into the regulatory mechanisms of ER stress, especially its dynamic interplay with pathways of cell death, provides a solid theoretical foundation for the discovery and validation of innovative drugs.

In summary, ER stress-related UPR components play a central role in the progression and treatment of NSCLC. It not only reflects the delicate balance of the intracellular environment but also serve as a critical link between the effectiveness of chemotherapeutics and decisions of cellular fate. In the future, through a deeper understanding of the molecular mechanisms of ER stress and their roles in drug responses, we will be able to design more precise and effective therapeutic strategies. This aims to improve the prognosis for NSCLC patients and heralds a new chapter in combating this stubborn form of cancer.

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Disclosure of conflict of interest

None.

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