

# The Role and Mechanism of Unfolded Protein Response Pathway in Tumor Drug Resistance

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**Abstract:** In the process of tumor proliferation and metastasis, tumor cells encounter hypoxia, low glucose, acidosis, and other stressful environments. These conditions prompt tumor cells to generate endoplasmic reticulum stress (ERS). As a signal mechanism that mitigates ERS in eukaryotic cells, the unfolded protein response (UPR) pathway can activate cells and tissues, regulating pathological activities in various cells, and maintaining ER homeostasis. It forms the most crucial adaptive and defensive mechanism for cells. However, under the continuous influence of chemotherapy drugs, the quantity of unfolded proteins and erroneous proteins produced by tumor cells significantly increases, surpassing the normal regulatory range of UPR. Consequently, ERS fails to function properly, fostering tumor cell proliferation and the development of drug resistance. This review delves into the study of three UPR pathways (PERK, IRE1, and ATF6), elucidating the mechanisms of drug resistance and research progress in the signal transduction pathway of UPR related to cancers. It provides a profound understanding of the role and relationship between UPR and anti-tumor drugs, offering a new direction for effective clinical treatment.

**Keywords:** Unfolded protein response (UPR); Tumor resistance; Activating transcription factor 6 (ATF6); Protein kinase RNA-like endoplasmic reticulum kinase (PERK); Inositol requiring enzyme 1 (IRE1)

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## 1. Introduction

In eukaryotic cells, the endoplasmic reticulum (ER) is a membranous organelle intricately woven throughout the cell, primarily responsible for the composition, folding, modification, and secretion of proteins. The ER, resembling a microcosm of the entire cell, operates as a dynamic system meticulously controlling the processes of protein synthesis and folding. Its homeostasis is finely tuned but susceptible to disruption. Various stimuli such as hypoxia, nutrient deficiency, high cell proliferation rates, abnormal redox homeostasis, or exposure to chemical drugs can prompt protein misfolding in the ER and the accumulation of unfolded proteins. An imbalance in ER homeostasis leads to a form of cellular disease. A protective stress response, preventing the

aggregation of unfolded proteins, is termed endoplasmic reticulum stress (ERS) <sup>[1]</sup>.

The unfolded protein response (UPR), functioning as a signaling mechanism to alleviate ERS in eukaryotic cells, is the primary reaction in numerous cascade pathways activated by ERS, extensively researched. The UPR pathway mobilizes cells and tissues to regulate the pathological activities of various cells, playing a pivotal role in safeguarding and restoring ER homeostasis. It forms the most crucial adaptability and defense mechanism for cells. When the ER's protein folding capacity is disrupted or cellular demands are excessive, misfolded proteins accumulate in the ER. At this juncture, the UPR transmits signals about the ER's health to the nucleus by upregulating the activity of several transcription factors. Post-UPR activation, these transcription factors elevate the expression of related genes, reestablishing protein homeostasis and restoring ER through multiple mechanisms: (1) transient attenuation of protein translation, (2) augmentation of protein folding capacity, and (3) clearance of unfolded/misfolded proteins through protein quality control systems <sup>[2]</sup>.

Overcoming ERS primarily depends on stress sensors that detect ERS: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) <sup>[3-6]</sup>. These three effector proteins can each activate their signaling cascades to induce UPR. In periods of low ERS, UPR activation correctly expresses folded proteins, alleviating the burden of ERS, safeguarding cells, promoting tumor cell survival, and preventing tumors from progressing adversely. Conversely, active tumor cells increase the demand for translation, modification, folding, and secretion of proteins in the ER, resulting in elevated ERS levels. Limited blood vessel supply cannot match the rapid tumor proliferation, restricting tumor growth. Uncontrolled tumor cell proliferation and metabolism compromise ER integrity, causing misfolded proteins and improper reflections in the membrane cavity. This, combined with imbalanced Ca<sup>2+</sup> distribution, triggers a novel endogenous apoptosis pathway, known as the ERS apoptosis pathway, inducing cell death <sup>[7-10]</sup>.

As research on UPR has deepened in recent years, elucidating the signal transduction pathways in UPR offers a new direction for understanding tumor drug resistance mechanisms and effective treatments <sup>[11]</sup>.

## 2. General mechanisms of tumor drug resistance

The mechanisms underlying tumor drug resistance are intricate and varied. Recent studies have underscored the significance of ERS as a potential influential factor in the drug resistance of tumor cells <sup>[9,10]</sup>. Moreover, the UPR plays a pivotal role in tumor progression and resistance to treatment <sup>[1,5,12-18]</sup>, involving processes such as DNA damage repair, apoptosis inhibition, autophagy, and more <sup>[18]</sup>.

In instances of DNA damage within tumors, UPR-regulated cells induced by ERS activate related recovery mechanisms to facilitate DNA repair. This ensures that the tumor microenvironment reaches a "steady state" during this period. Most anti-tumor drugs inflict damage on cellular DNA, leading to a reduction in the proportion of unfolded and misfolded proteins produced through cellular transcription and translation. This disruption affects the intracellular protein balance and compromises the adaptation of ERS. The UPR, however, can override the original adaptive environment, reasserting its role. Consequently, it maintains cellular protein balance and accelerates the induction of cell apoptosis.

Nevertheless, with the sustained use of chemotherapeutic drugs, the increase in DNA damage corresponds to an escalation in DNA repair function. The unfolded and misfolded proteins produced during post-transcriptional translation undergo a significant surge, surpassing the normal regulatory range of UPR. The adaptability of ERS is severely impaired once again, rendering it incapable of functioning normally. This ultimately promotes tumor cell proliferation and the development of drug resistance.

In summary, ERS exhibits a dual role: it can activate early cancer cells while also contributing to the

transformation of late-stage cancer cells into drug-resistant entities <sup>[19]</sup>.

## 2.1. The role of the PERK-ATF4 pathway in tumor drug resistance

PERK functions as a eukaryotic translation initiation factor 2 (eIF2 $\alpha$ ) and belongs to the upstream kinase family. It is a type I transmembrane protein housing a serine/threonine kinase domain, constituting the most crucial pathway in the UPR against ERS <sup>[20,21]</sup>. ATF4, a stress-induced transcription factor, also known as cyclic AMP (cAMP)-linked response element 2 (CREB2), holds a pivotal role in the integrated stress response pathway <sup>[21]</sup>. Controlling a wide array of adaptive genes, ATF4 equips cells to withstand stress.

Upon ERS in eukaryotic cells, numerous unfolded or misfolded proteins set off a series of reactions. This prompts PERK to oligomerize and activate in the ER membrane, inducing cell phosphorylation and activating the kinase domain. This, in turn, promotes the upregulation of ATF4 expression, aiding tumor cells in recognizing and processing external stimuli. It enhances their adaptability to adverse factors in the surroundings, effectively resisting external damage, and consequently, fostering the survival and spread of tumors <sup>[22,23]</sup>. However, under prolonged stress conditions, ATF4 promotes the induction of apoptosis <sup>[24]</sup>.

Compared to normal tissues, ATF4 is up-regulated in tumor cells. As a vital member of the transcription factor family, its primary function is to activate the transcription of genes related to oxidative stress response, amino acid synthesis, cell differentiation, angiogenesis, and other processes regulating tumor progression. This suggests that ATF4 may present a novel opportunity for tumor treatment <sup>[22,25,26]</sup>.

UPR activates the PERK-eIF2 $\alpha$ -ATF4 pathway, resulting in the constitutive activation of PERK signaling at the epithelial-mesenchymal transition (EMT), inducing malignant tumors <sup>[27]</sup>. Although PERK inhibition does not affect EMT cell survival or growth, research indicates that inhibiting PERK activity heightens EMT cell sensitivity to ERS. EMT cells rely on PERK signaling to form tumors and migrate. Additionally, both dedifferentiated cancer cells and cancer stem-like cells generated by EMT exhibit resistance to various chemotherapy treatments <sup>[28]</sup>. Extensive experimental data indicates a robust positive correlation between the expression of EMT genes and PERK pathway genes.

The PERK-eIF2 $\alpha$ -ATF4 pathway has been suggested to play a crucial role in promoting tumor cell apoptosis and resistance to chemotherapeutic drugs. This has been explored in various diseases, including ovarian cancer, colorectal cancer, pancreatic cancer, breast cancer, and cervical cancer, among others <sup>[29-33]</sup>. Notably, Shi *et al.* discovered an upregulation of PERK-eIF2 $\alpha$ -ATF4 pathway activity in colon cancer cells, leading to increased resistance to 5-fluorouracil (5-FU). Genetic intervention or pharmacological inhibition of this pathway effectively heightened the sensitivity of colorectal cancer cells to 5-FU in mouse experiments, offering promise in overcoming chemotherapy drug resistance in colorectal cancer <sup>[29]</sup>. Subsequent studies revealed that inhibiting PERK accelerated the apoptosis of colon cancer cells, reducing the expression of eIF2 $\alpha$  and ATF4, thereby increasing cancer cell sensitivity to 5-FU <sup>[32]</sup>.

Acriflavine was found to inhibit the PERK-eIF2 $\alpha$ -ATF4 pathway by blocking eIF2 $\alpha$  phosphorylation and reducing ATF4 translation. This restoration effectively revived drug sensitivity in acquired drug-resistant pancreatic cancer cell lines <sup>[34,35]</sup>. Consequently, targeting the PERK-eIF2 $\alpha$ -ATF4 pathway holds promise in diminishing or inhibiting tumor cell drug resistance, improving the efficacy of drug chemotherapy, and enhancing patient prognosis.

## 2.2. The role of the IRE1 $\alpha$ -XBP1 pathway in tumor drug resistance

Similar to PERK, IRE1 is a type I transmembrane protein featuring a serine/threonine kinase domain and an endoribonuclease domain situated on the cytoplasmic side of the protein. As a primary pathway in the

UPR, the IRE1 $\alpha$ -XBP1 pathway has received extensive study. Following UPR activation by ERS, IRE1 $\alpha$  is activated, inducing the cleavage of the transcription factor splicing X-box binding protein 1 (XBP1) mRNA. This process generates the XBP1 variant (XBP1s), initiating a series of gene transcription events. These genes primarily contribute to protein refolding or promote the degradation of unfolded proteins, positively regulating ER chaperones, genes encoding endoplasmic reticulum-associated protein degradation (ERAD), and liposome metabolism. Consequently, this eases the pressure on the ER [20].

Continual stimulation of IRE1 $\alpha$ -XBP1 signaling can trigger tumor cell proliferation, metastasis, and chemoresistance. However, existing pharmacological technologies face limitations in producing effective XBP1 inhibitors. Consequently, targeting its upstream regulator, IRE1 $\alpha$ , presents a potential new avenue for tumor treatment [36]. IRE1 $\alpha$  inhibitor was discovered to significantly inhibit the proliferation of breast tumor cells. Furthermore, the combination of the IRE1 $\alpha$  inhibitor MKC 8866 and paclitaxel effectively enhanced its efficacy in triple-negative breast cancer, leading to improved therapeutic effects. This underscores that the expression of XBP1 impacts the treatment resistance of tumors, offering breakthroughs in cancer drug resistance research [37-39].

Endocrine therapy often leads to drug resistance in breast cancer patients, resulting in disease progression and mortality. Targeting XBP1 is considered a promising approach to overcoming endocrine drug resistance in breast cancer. Ming *et al.* observed up-regulation of XBP1 at the mRNA and protein levels in breast cancer cells. The IRE1 $\alpha$  inhibitor, STF-083010, in combination with tamoxifen, significantly reversed endocrine resistance in breast cancer. This improved the response of tumor cells to chemotherapy drugs, enhancing the therapeutic effect [40].

In summary, treatment resistance frequently allows cancer cells to evade the effects of monotherapy. The IRE1 $\alpha$ -XBP1 pathway may play a role in tumor cell resistance. The combined use of IRE1 $\alpha$  inhibitors and chemotherapy drugs can effectively enhance the efficacy of chemotherapy drugs and alter the drug resistance of tumor cells [20].

### 2.3. The role of ATF6 in tumor drug resistance

ATF6, a type II transmembrane glycoprotein and transcriptional activator, plays a pivotal role in initiating UPR signaling during ERS. When unfolded proteins are detected, full-length ATF6 (p90) undergoes transportation to the Golgi apparatus for processing and cleavage. The cleaved p90 releases the N-terminal cAMP-dependent ATF6 alpha form (p50) into the cytoplasm, translocates to the nucleus, binds to DNA on the endoplasmic reticulum stress response element (ERSE), and regulates ERAD and UPR genes.

Recent studies have identified ATF6 as playing a crucial role in tumor drug resistance, making it a potential new target. High-grade serous ovarian cancer (HGSOC), the most lethal ovarian cancer histotype, faces limited treatment options for chemotherapy-resistant disease. Elevated ATF6 expression in HGSOC has been linked to poor survival rates, particularly in the context of resistance to poly-ADP ribose polymerase (PARP) inhibitors. Targeted treatment of PARP inhibitors, along with RNA sequencing and short hairpin RNA (shRNA) screening, has established ATF6 as a mediator of DNA damage response and PARP inhibitor resistance [41].

In the case of gastric cancer drug resistance, ER and autophagy are recognized mechanisms. Research on the JAK2/STAT3 pathway in 5-FU-resistant AGS cells revealed that agents inhibiting JAK2 or STAT3 significantly altered protein expression and suppressed ATF6 promoter activity. Targeting the JAK2/STAT3 pathway emerges as a potential strategy to diminish cancer resistance to 5-FU, offering new insights into the molecular mechanisms of gastric cancer resistance to this drug [36].

Benedetti's team recently uncovered that inhibiting ATF6 enhances the anticancer effect of DNA-damaging agents. Doxorubicin, a widely used DNA-damaging drug for colon cancer treatment, exhibited increased

cytotoxicity in ERS cancer cells when ATF6 is inhibited. This suggests a potential strategy to sensitize colon cancer cells to the cytotoxic effects of doxorubicin, promoting cell death <sup>[42]</sup>.

### 3. Summary

Tumors adeptly regulate their protein folding capabilities through the ERS response pathway, flourishing even in adverse conditions such as hypoxia, nutrient deprivation, and oxidative stress. Activation of multiple ERS sensors has been identified as a driver for the proliferation, metastasis, and drug resistance of malignant tumors. Notably, tumor drug resistance poses a significant challenge, limiting the efficacy of chemotherapy drugs in tumor treatment. Integrating anti-tumor drugs with regulatory factors and effectors targeting ERS can significantly enhance the sensitivity of tumor cells to drugs, leading to more effective treatment outcomes.

Current research underscores the distinct biological functions of the three UPR pathways – PERK, IRE1, and ATF6 – in regulating cell survival or apoptosis. These pathways, in turn, exert downstream effects on abnormal DNA repair, apoptosis control, and autophagy, each playing a unique role in influencing biological functions <sup>[25]</sup>. Despite the incomplete understanding of ERS and its related anti-cancer mechanisms, delving into the anti-cancer activity triggered by UPR and the intricate interactions between them is essential. This in-depth exploration is crucial for identifying more effective anti-cancer solutions and developing novel drugs, fostering the advancement of translational medicine.

In conclusion, a heightened comprehension of drug resistance mechanisms holds the key to reversing drug resistance in solid tumor cells, paving the way for innovative clinical drug treatments for solid tumors.

### Disclosure statement

The authors declare no conflict of interest.

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