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Endoplasmic Reticulum Stress and the Unfolded Protein Response in Cancer Drug Resistance: Mechanisms and Therapeutic Opportunities

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Abstract. Endoplasmic reticulum stress (ERS) is increasingly recognized as a key regulator of cancer cell adaptation and treatment resistance. When misfolded proteins accumulate in the ER lumen, the unfolded protein response (UPR) is activated through three major branches: PERK, IRE1α, and ATF6. In cancer, moderate or chronic UPR activation can promote cell survival by reducing protein toxicity stress, reprogramming metabolism, maintaining redox balance, and remodeling the tumor microenvironment. However, severe or unrelieved ERS can over-activate UPR, leading to apoptosis, immunogenic cell death and inflammatory response. This review systematically discusses the mechanism of cell-autonomous and non-cell-autonomous roles of ERS in cancer drug resistance, focusing on the molecular mechanisms of UPR-driven intrinsic adaptability, metabolic reprogramming, endoplasmic reticulum-mitochondrial interaction, and immunosuppressive remodeling in tumor microenvironment. In addition, the article also discusses the therapeutic strategies targeting UPR, the clinical application potential of ERS-related biomarkers, and the design principles of combined treatment regimens, aiming to provide theoretical reference and potential intervention targets for precise anticancer therapy.

Keywords: Endoplasmic Reticulum Stress, Unfolded Protein Response, Cancer Drug Resistance, Tumor Microenvironment, Targeted Therapy

1. Introduction

The endoplasmic reticulum (ER) is an important organelle for protein folding, lipid synthesis, and calcium storage. When conditions such as hypoxia, nutrient shortage, or metabolic imbalance disturb ER homeostasis, unfolded or misfolded proteins can accumulate, leading to endoplasmic reticulum stress (ERS) [1]. Cells respond through the unfolded protein response (UPR), which is mainly regulated by three ER membrane sensors, including protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) [2]. Under normal conditions, these sensors are restrained by the chaperone binding immunoglobulin protein/glucose-regulated protein 78 (BiP/GRP78); during stress, BiP dissociation helps initiate signaling that either restores ER function or, under severe stress, contributes to cell death [3].

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Drug resistance remains a major barrier to effective cancer therapy. The tumor microenvironment exposes cancer cells to persistent and mild stress, and this can constitutively induce ERS and sustained UPR in malignant cells [4]. Sustained UPR signaling helps tumor cells adapt to treatment pressure, thereby promoting survival, metabolic flexibility, and immune escape [5, 6].

For this reason, ERS has become an important therapeutic focus in oncology. Current strategies generally seek either to weaken the adaptive, pro-survival arms of the UPR or to drive stress beyond the level that cancer cells can tolerate [6, 7]. This dual possibility makes ERS especially relevant for understanding both treatment failure and new therapeutic opportunities. Figure 1 summarizes the three branches of UPR (PERK, IRE1α, and ATF6) in cancer, and shows how these signaling pathways promote cell adaptation and survival when moderately activated, or induce apoptosis when overactivated.

This review hence examines how ERS contributes to cancer drug resistance and discusses cell-autonomous/non-cell-autonomous mechanisms in the tumor microenvironment. It summarizes emerging clinical strategies. The goal is to identify UPR-related vulnerabilities that may provide more precise cancer treatment.

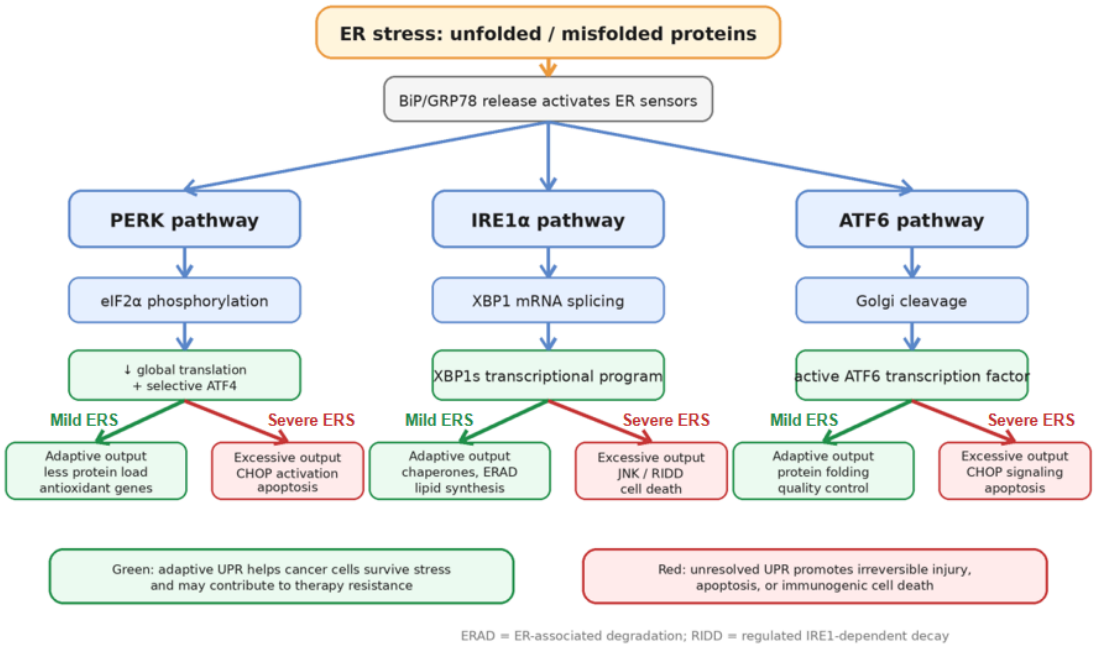


Figure 1. Three-branch model of the UPR in cancer. [green arrows summarize adaptive signaling that reduces protein-folding stress and supports tumor cell survival, whereas red arrows indicate unresolved signaling that promotes C/EBP homologous protein (CHOP) activation, c-Jun N-terminal kinase/regulated IRE1-dependent decay (JNK/RIDD) signaling, apoptosis, or immunogenic cell death (ICD). BiP/GRP78 is the ER chaperone whose release turns on the sensors; eukaryotic initiation factor 2α (eIF2α) phosphorylation slows translation, X-box binding protein 1 (XBP1) splicing produces XBP1s, and Golgi cleavage activates ATF6.]

2. Cell-autonomous mechanisms: intrinsic adaptation within cancer cells

The survival of cancer cells in the stressful tumor microenvironment depends in part on their ability to use the ERS response as an internal survival system. Recent reviews suggest that, in cancer, the UPR often shifts from a short-term repair pathway to a long-term program that supports adaptation

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and drug resistance [8]. To better understand this survival shift, the following three mechanisms inside cancer cells can be discussed in order.

One important cell-autonomous mechanism is the ability of the UPR to balance cell protection and cell death. When ERS is moderate or temporary, the three main UPR pathways help cancer cells restore ER homeostasis and survive [1, 2]. The PERK pathway reduces general protein translation through eIF2α phosphorylation, which lowers the number of new proteins entering the ER while allowing selective translation of stress-adaptive factors such as ATF4 [1, 2]. The IRE1α pathway splices XBP1 mRNA to produce XBP1s, a transcription factor that increases the expression of genes involved in protein folding, ER-associated degradation, and lipid synthesis [2, 3]. The ATF6 pathway moves to the Golgi and is cleaved into an active transcription factor that promotes chaperone expression and ER quality-control capacity [2]. Together, these pathways protect cancer cells by reducing proteotoxic pressure, improving folding capacity, and supporting adaptation to therapy-induced stress [6-8]. However, if ERS is too strong or remains unresolved, the same UPR network can shift from a protective program to a pro-death response. Persistent PERK-ATF4 signaling can increase CHOP expression, which promotes apoptosis by disturbing B-cell lymphoma 2 (BCL-2) family signaling, oxidative balance, and calcium homeostasis [7, 9]. Sustained IRE1α activation can also contribute to cell death through stress kinase signaling and the degradation of selected RNAs [3, 6]. Therefore, the UPR acts as a stress-response switch in cancer cells: moderate activation supports survival and drug resistance, whereas excessive or prolonged activation can push cells toward irreversible damage and apoptosis [1, 6-8].

ERS also promotes metabolic and redox rewiring that protects cancer cells from oxidative injury. In particular, the PERK-eIF2α-ATF4 axis acts as a central regulator of the integrated stress response. Long-term activation of ATF4 increases the expression of genes involved in amino acid metabolism and antioxidant defense. For example, ATF4 can increase the expression of SLC7A11, the cystine/glutamate antiporter xCT, which supports glutathione synthesis and helps neutralize reactive oxygen species (ROS) generated by radiotherapy or platinum-based drugs. The eIF2α/ATF4 pathway is also required for the expression of important autophagy-related genes such as ATG5 and MAP1LC3B, thereby supporting nutrient recycling and metabolic flexibility during starvation [10]. At the same time, the IRE1α-XBP1s branch can activate lipid biosynthetic programs, helping the ER expand its membrane system to handle increased protein production [11].

Finally, the ER-Mitochondria Connection is an important internal mechanism for maintaining bioenergetics. The contact sites between these organelles, known as mitochondria-associated endoplasmic reticulum membranes, serve as channels for calcium (Ca^{2+}) signaling. During moderate, survival-oriented ERS, Ca^{2+} is released from the ER through inositol 1,4,5-trisphosphate receptor (IP3R) channels and transferred into mitochondria through the IP3R-GRP75-voltage-dependent anion channel 1 (VDAC1) complex. Inside mitochondria, Ca^{2+} activates key enzymes of the TCA cycle, such as pyruvate dehydrogenase, and helps sustain adenosine triphosphate (ATP) production. Many cancer cells are highly dependent on this continuous ER-to-mitochondria Ca^{2+} transfer, because it helps prevent excessive AMPK-driven autophagy and supports survival [12]. By adjusting this communication between organelles, cancer cells can use ER-derived signals to avoid activating cell death pathways [8].

3. Non-cell-autonomous mechanisms: reshaping the tumor microenvironment

The effects of ERS are not limited to the inside of cancer cells. It also drives non-cell-autonomous changes that reshape the tumor microenvironment into an immunosuppressive setting. An important concept here is stress transmission, also called transmissible ERS. Stressed tumor cells can pass

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stress-related signals to nearby healthy cells, especially myeloid cells. Tumor cells release soluble factors, which can activate UPR in macrophages and dendritic cells [13]. This stress transmission promotes immune cells to turn to a pro-inflammatory but tumor-supporting phenotype, including the production of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which helps to build a microenvironment conducive to tumor growth and survival [11].

Meanwhile, ERS greatly promotes immunosuppression by weakening the anti-tumor immune response. There is severe metabolic competition in the tumor microenvironment. Hypoxia and nutritional deprivation trigger ERS in infiltrating immune cells. The IRE1α-XBP1 pathway is continuously activated in tumor-associated dendritic cells. This leads to significant changes in lipid metabolism, causing abnormal lipid droplet accumulation, thereby interfering with antigen processing and its presentation to T lymphocytes (T cells) [14]. T cell-mediated immunity is thus weakened. In T cells themselves, persistent UPR activation induced by glucose deprivation reduces effector function and increases the expression of depletion markers (such as programmed cell death protein 1), making it easier for tumors to evade immune surveillance [11].

The main features of the tumor microenvironment, especially acidity and hypoxia, further enhance these non-cell-autonomous effects through feedback loops. In response to ERS, cancer cells often turn to glycolysis, resulting in increased lactic acid and proton release. This acidifies the extracellular space and directly weakens the cytolytic activity of natural killer cells and cytotoxic T lymphocytes. Acid-induced autophagy regulated by ERS sensors can protect lung cancer cells from apoptosis under low pH conditions, and also reduce the metabolic adaptability of infiltrating immune cells [15].

Hypoxia-induced activation of the PERK pathway helps to support selective translation of pro-survival and angiogenic factors. The PERK-eIF2α pathway is essential to help tumor cells tolerate extreme hypoxia by allowing selective translation of mRNAs involved in hypoxia adaptation [16]. This connection means that as tumors grow and oxygen is limited, the ERS response helps to reshape the surrounding environment in a way that supports sustained growth [8]. By integrating these external signals, ERS acts as a central hub for the co-evolution of tumors and their microenvironment [11].

4. Clinical translation: how ERS can be targeted in treatment

A key issue is how to translate these ERS mechanisms into therapeutic strategies. In practice, the goal is not just to block every UPR signal. On the contrary, researchers are trying to target the most dependent pathway parts of cancer cells while retaining normal stress responses in healthy tissues. According to the current research, four directions are particularly important, which are protein degradation agents, ICD, biomarkers and direct therapy based on the UPR [6, 17].

The first possible strategy is to use protein degradation agents, such as proteolysis-targeting chimeras (PROTACs). Unlike common inhibitors that can only temporarily block protein activity, PROTACs aim to remove the target protein itself through a cellular degradation mechanism. This approach is attractive in cancer because it may reduce signal transduction more completely and may help overcome some forms of drug resistance. In the field of endoplasmic reticulum stress, this idea is still in development, but it provides a useful framework for eliminating the stress-supporting proteins on which tumor survival depends [17].

Another promising direction is to trigger ICD through strong or sustained ERS. When ERS becomes too intense, cancer cells may not only die, but also release danger signals that make the immune system respond more actively. For example, ERS-related ICD is often associated with calreticulin exposure and the release of ATP or HMGB1, which can help dendritic cells and T cells

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recognize the tumor. For this reason, treatments that combine ERS induction with immunotherapy may improve anti-tumor effects in some patients [18, 19].

A third translational direction is the development of biomarkers. Since ERS is dynamic and changes during treatment, markers related to the UPR may help clinicians judge whether a tumor is adapting, responding, or becoming resistant. GRP78 is one of the most studied candidates in this area. It can be overexpressed on the tumor cell surface and, in some settings, may also be detected in blood-based samples, suggesting possible value for diagnosis, treatment monitoring, or patient stratification [20, 21]. Although these biomarkers are not yet routine in clinical care, they provide an important bridge between laboratory findings and personalized medicine.

More broadly, UPR-based therapy remains an important long-term goal. Small-molecule inhibitors against PERK, IRE1α, or related downstream signals are already being explored, often in combination with chemotherapy, targeted therapy, or immune therapy. The main challenge is that the UPR has a dual role: moderate activation helps cells survive, but excessive activation can drive cell death. Therefore, future treatment design will likely depend on choosing the right pathway, the right tumor type, and the right treatment window, rather than applying the same ERS strategy to every cancer [5, 6, 8].

5. Conclusion and future perspectives

In summary, ERS is not a simple cellular stress response, but a core adaptation mechanism throughout the whole process of tumor progression. On the one hand, the synergistic activation of the three branches of UPR enables cancer cells to survive under the multiple pressures of protein folding load, metabolic environment fluctuation and therapeutic intervention. On the other hand, ERS signals can also cross cell boundaries and reshape the tumor microenvironment through stress transmission, that is, from inducing immune cell function exhaustion to using hypoxia and acidic environment to form positive feedback to strengthen its own tumor promoting effect. This dual regulation of "intrinsic cellular adaptation" and "exogenous remodeling of microenvironment" constitutes the basis of ERS-driven cancer drug resistance.

These findings also reveal a seemingly contradictory transformation dilemma, i.e., UPR can not only help cancer cells tolerate treatment stress, but also trigger apoptosis or immunogenic death when stress is overloaded. Therefore, the core challenge of targeting ERS is not simply to inhibit or activate, but how to accurately push UPR signals in a direction that is detrimental to tumors. At present, most of the small molecule inhibitors for PERK and IRE1α are still in the preclinical stage, and their therapeutic window (i.e., the safe range between effective dose and toxic dose) and the possible adaptive drug resistance of tumors after long-term use have not been systematically evaluated. In this regard, GRP78 as a potential biomarker is worthy of attention. Its overexpression on the surface of tumor cells not only reflects the activation level of ERS, but also may provide a basis for patient stratification and efficacy monitoring.

In addition, the following directions are also worth exploring in the future. First, it is necessary to clarify how to determine the optimal timing of UPR intervention according to tumor type and disease stage. The dependence of different cancers on ERS is different. Some tumors (such as multiple myeloma, pancreatic cancer) are inherently in a high ERS state, and may be more suitable for the "push over threshold" strategy; other tumors may need to block adaptive signals. Second, in the era of immunotherapy, whether it is possible to develop interventions that specifically block adaptive UPR in cancer cells without interfering with normal immune cell function requires a more in-depth analysis of the differential role of ERS in different immune cell subsets. Third, the combination of ERS modulators with existing chemotherapy, targeted drugs or immune checkpoint

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inhibitors is worthy of accelerated validation in preclinical models and early clinical trials. Only by making substantial breakthroughs on the above issues can the treatment strategies for ERS truly move from the laboratory to the clinic and provide new solutions to overcome cancer resistance.

References

[1] Hetz, C., and Papa, F. R. (2018) The Unfolded Protein Response and Cell Fate Control. Molecular Cell, 69(2), 169-181.

[2] Read, A., and Schröder, M. (2021) The Unfolded Protein Response: An Overview. Biology, 10(5), 384.

[3] Adams, C. J., Kopp, M. C., Larburu, N., Nowak, P. R., and Ali, M. M. U. (2019) Structure and Molecular Mechanism of ER Stress Signaling by the Unfolded Protein Response Signal Activator IRE_1. Frontiers in Molecular Biosciences, 6(11).

[4] Chen, X., and Cubillos-Ruiz, J. R. (2021) Endoplasmic Reticulum Stress Signals in the Tumour and Its Microenvironment. Nature Reviews Cancer, 21(2), 71-88.

[5] Yadav, R. K., Chae, S.-W., Kim, H.-R., and Chae, H. J. (2014) Endoplasmic Reticulum Stress and Cancer. Journal of Cancer Prevention, 19(2), 75-88.

[6] Ojha, R., and Amaravadi, R. K. (2017) Targeting the Unfolded Protein Response in Cancer. Pharmacological Research, 120, 258-266.

[7] Oakes, S. A. (2020) Endoplasmic Reticulum Stress Signaling in Cancer Cells. The American Journal of Pathology, 190(5), 934-946.

[8] Ghemrawi, R., Kremesh, S., Mousa, W. K., and Khair, M. (2025) The Role of ER Stress and the Unfolded Protein Response in Cancer. Cancer Genomics & Proteomics, 22(3), 363-381.

[9] Hu, H., Tian, M., Ding, C., and Yu, S. (2019) The C/EBP Homologous Protein (CHOP) Transcription Factor Functions in Endoplasmic Reticulum Stress-Induced Apoptosis and Microbial Infection. Frontiers in Immunology, 9, 3083.

[10] B'chir, W. et al. (2013) The eIF2α/ATF4 Pathway Is Essential for Stress-Induced Autophagy Gene Expression. Nucleic Acids Research, 41(16), 7683-99.

[11] Cubillos-Ruiz, J. R., Bettigole, S. E., and Glimcher, L. H. (2017) Tumorigenic and Immunosuppressive Effects of Endoplasmic Reticulum Stress in Cancer. Cell, 168(4), 692-706.

[12] Cárdenas, C. et al. (2016) Selective Vulnerability of Cancer Cells by Inhibition of Ca2+ Transfer from Endoplasmic Reticulum to Mitochondria. Cell Reports, 14(10), 2313-2324.

[13] Mahadevan, N. R., Rodvold, J., Sepulveda, H., Rossi, S., Drew, A. F., and Zanetti, M. (2011) Transmission of Endoplasmic Reticulum Stress and Pro-Inflammation from Tumor Cells to Myeloid Cells. Proceedings of the National Academy of Sciences of the United States of America, 108(16), 6561-6566.

[14] Cubillos-Ruiz, J. R. et al. (2015) ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis. Cell, 161(7), 1527-1538.

[15] Xie, W.-Y., Zhou, X.-D., Li, Q., Chen, L.-X., and Ran, D.-H. (2015) Acid-Induced Autophagy Protects Human Lung Cancer Cells from Apoptosis by Activating ER Stress. Experimental Cell Research, 339(2), 270-279.

[16] Bi, M. et al. (2005) ER Stress-Regulated Translation Increases Tolerance to Extreme Hypoxia and Promotes Tumor Growth. The EMBO Journal, 24(19), 3470-3481.

[17] Zhao, L., Zhao, J., Zhong, K., Tong, A., and Jia, D. (2022) Targeted Protein Degradation: Mechanisms, Strategies and Application. Signal Transduction and Targeted Therapy, 7(1), 113.

[18] Kepp, O. et al. (2013) Crosstalk Between ER Stress and Immunogenic Cell Death. Cytokine & Growth Factor Reviews, 24(4), 311-318.

[19] Rodrigues, M. C. et al. (2022) An Overview on Immunogenic Cell Death in Cancer Biology and Therapy. Pharmaceutics, 14(8), 1564.

[20] Farshbaf, M., Khosroushahi, A. Y., Mojarad-Jabali, S., Zarebkohan, A., Valizadeh, H., and Walker, P. R. (2020) Cell Surface GRP78: An Emerging Imaging Marker and Therapeutic Target for Cancer. Journal of Controlled Release, 328, 932-941.

[21] Raiter, A., Lipovetzki, J., Lubin, I., and Yerushalmi, R. (2020) GRP78 Expression in Peripheral Blood Mononuclear Cells Is a New Predictive Marker for the Benefit of Taxanes in Breast Cancer Neoadjuvant Treatment. BMC Cancer, 20, 333.