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How Cancer Cells Exploit Unfolded Protein Response Signaling for Survival, Metastasis, and Therapy Resistance

Zihe Zhou

University of Macau, Macau, China
zhouzihe59@gmail.com

Abstract. The unfolded protein response (UPR) is a homeostatic protective mechanism activated in response to endoplasmic reticulum (ER) stress. However, once co-opted by cancer cells, its function extends far beyond maintaining proteostasis and becomes an important regulator of tumor progression. This review summarizes how the three canonical UPR branches establish a persistent adaptive state under chronic ER stress. It discusses the molecular mechanisms by which UPR signaling maintains proteostasis, reprograms cellular metabolism, alleviates oxidative stress, and coordinates autophagy. Thereby it allows cancer cells to survive in hostile microenvironments. The review further examines how these adaptive programs support tumor metastasis by promoting anoikis resistance, epithelial-mesenchymal plasticity, and tumor dormancy, which also enhances resistance to chemotherapy and immunotherapy. Current evidence suggests that cancer cell survival, metastasis, and therapy resistance are not independent consequences of UPR activation, but interconnected manifestations of a unified stress adaptation strategy driven by the UPR. By clarifying how cancer cells exploit UPR signaling and its underlying mechanisms, this review aims to provide insights into potential specific therapeutic opportunities for cancer.

Keywords: ER Stress, UPR, Proteostasis, Metastasis, Therapy Resistance

1. Introduction

Proteins are vital components of life. In eukaryotic cells, the synthesis, folding and modifying of proteins all occur in the endoplasmic reticulum (ER) [1]. This process is intricate and dependent on the redox state, calcium homeostasis, energy supply, and the chaperone system within the ER lumen. The occurrence of certain external factors or intracellular events can result in the accumulation of misfolded or unfolded proteins within the ER, a condition known as ER stress [2]. By contrast to normal cells and tissues, tumor cells are more prone to experience persistent ER stress. The tumor microenvironment is a harsh and dynamic environment in which rapid and uncontrolled tumor cell proliferation frequently outpaces the development of functional blood vessels [3]. This angiogenic mismatch results in impaired perfusion and establishes a microenvironment characterized by hypoxia and nutrient deprivation, thereby inducing persistent ER stress. In addition, lactate accumulation, elevated reactive oxygen species (ROS), and the excessive transcriptional, translational, and secretory demands imposed by oncogenic signaling further aggravate ER stress.

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Under these conditions, the unfolded protein response (UPR) becomes a critical adaptive network that supports tumor cell remodeling and survival.

UPR is an evolutionarily conserved signaling network that monitors protein-folding conditions within the ER [2]. In mammalian cells, the UPR is primarily mediated by three classical ER transmembrane sensors: inositol-requiring enzyme 1α (IRE1α), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6). They have been demonstrated to alleviate ER overload and restore cellular adaptability by temporarily suppressing protein translation, enhancing the expression of chaperones and the ER-associated degradation (ERAD) system and inducing autophagy [2]. In nature, UPR is an adaptive reaction to protect cells or tissues. However, under the context of tumors, the biological significance of UPR exceeds general cell protection. Unlike typical transient stress responses that restore homeostasis, UPR activation in tumors often leads to a sustained and non-lethal state. In this state, the UPR is exploited by tumors in the long term, transferring an adaptive tool that supports their survival and malignant progression.

Furthermore, different intensities of ER stress led to distinct cellular outcomes. Moderate ER stress primarily activates the IRE1α–X-box binding protein 1 (XBP1) and PERK–ATF4 pathways to promote tumor cell survival, proliferation, and therapeutic tolerance by maintaining proteostasis, reprogramming metabolism, and enhancing antioxidant capacity [2]. In contrast, excessive ER stress exceeds the adaptive threshold and induces apoptosis through C/EBP homologous protein (CHOP) upregulation and caspase activation, while severe and irreversible stress may further trigger excessive autophagy, leading to cell death [4]. Therefore, the role of the UPR in cancer depends not only on its activation, but also on the intensity and duration of ER stress, as well as its interplay with autophagy.

Based on the context above, this review will focus on an oncology question: how cancer cells utilize UPR signaling to achieve survival, metastasis, and resistance to therapy. To address this main line of inquiry, this article will first outline the IRE1α, PERK, and ATF6 classical pathways alongside their specific exploitable functions in malignancy. Then it discusses in depth how the UPR systematically supports cancer cell survival under chronic strain, how these mechanisms extend to drive metastatic invasion, dormancy, and persistence, and how they ultimately enable profound resistance to modern anti-cancer therapies. Finally, it will analyze how these very same survival networks reveal actionable therapeutic targets. By clarifying how cancer cells exploit UPR signaling and its underlying mechanisms, this review aims to provide insights into potential specific therapeutic opportunities for cancer.

2. Canonical UPR signaling pathways

The ability of cancer cells to survive from chronic ER stress largely depends on their capacity to exploit the UPR. Under physiological conditions, the three canonical UPR sensors, IRE1α, PERK, and ATF6, are maintained in an inactive state through association with the ER chaperone immunoglobulin heavy-chain binding protein (BiP)/glucose-regulated protein 78 (GRP78) [2]. BiP/GRP78 is the major ER-resident molecular chaperone and a central regulator of protein-folding homeostasis within the ER. Under physiological conditions, BiP binds to the luminal domains of IRE1α, PERK, and ATF6, maintaining these stress sensors in an inactive state. Accumulation of unfolded proteins sequesters BiP away from these sensors, triggering their activation and initiating adaptive signaling programs designed to restore ER homeostasis. Although originally evolved as a protective response against proteotoxic stress, mounting evidence indicates that tumors frequently co-opt these pathways to sustain growth under hostile microenvironmental conditions [5].

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2.1. IRE1α-XBP1 axis: expanding adaptive capacity under stress

Among the three UPR branches, the IRE1α–XBP1 axis is one of the most evolutionarily conserved signaling branch [6]. Upon activation, IRE1α undergoes oligomerization and trans-autophosphorylation, leading to activation of its endoribonuclease domain. Its best-characterized substrate is XBP1 mRNA, which undergoes unconventional splicing to generate the potent transcription factor XBP1s [7]. XBP1s subsequently induces numerous genes involved in protein folding, ERAD, secretory pathway expansion and lipid biosynthesis [8]. And during this time, activated IRE1α can degrade selected mRNAs through regulated IRE1-dependent decay (RIDD), thereby reducing the ER protein-folding burden and contributing to the restoration of ER homeostasis.

In normal conditions, these functions appear to represent simple housekeeping activities. However, in tumors they acquire a much broader significance. Cancer cells often experience excessive protein synthesis driven by oncogenic pathways and therefore require an expanded protein-folding capacity to avoid proteotoxic collapse. In this context, the IRE1α–XBP1 pathway functions less like an emergency repair system and more like a transcriptional reprogramming platform. A study demonstrated that XBP1 is essential for cellular survival under hypoxic conditions and is required for efficient tumor growth in vivo [8]. Also, research showed that XBP1 directly cooperates with hypoxia-inducible factor 1α (HIF1α) in triple-negative breast cancer, driving hypoxia-responsive transcriptional programs and promoting tumor progression [9]. These findings illustrate that a pathway originally dedicated to ER homeostasis might be repurposed to support malignant adaptation.

2.2. PERK–eIF2α–ATF4 axis: balancing adaptive survival and apoptosis

PERK–eukaryotic initiation factor 2α (eIF2α)–ATF4 axis provides a complementary strategy compared to IRE1α–XBP1 axis. It primarily functions as a load-reduction and stress-tolerance network. Following its activation via autophosphorylation, PERK directly phosphorylates the alpha subunit of eIF2α at serine 51 [10]. This critical phosphorylation event prevents the assembly of the eIF2-GTP-Met-tRNAi translation complex, culminating in a profound attenuation of global cap-dependent protein translation. This temporary translation block provides an immediate reprieve by restricting the influx of nascent polypeptide chains into the already congested ER lumen. However, despite this generalized translational shutdown, selected mRNAs featuring inhibitory upstream open reading frames experience enhanced selective translation [11]. Among these mRNAs, the most notable one is ATF4. Once expressed, ATF4 operates as a powerful transcriptional activator that upregulates genes driving amino acid import and biosynthesis, intracellular redox homeostasis, and the initiation of cytoprotective autophagy. Through this axis, tumor cells achieve resistance against nutrient deprivation and severe oxidative stress, turning a transient emergency program into an enduring survival infrastructure.

However, the PERK axis features a distinct biphasic nature. When ER stress becomes severe and unresolvable, this pathway switches from a pro-survival to a pro-apoptotic program. Under irreversible proteotoxic stress, continuous ATF4 activation strongly induces the transcription of CHOP. As a core pro-apoptotic transcription factor, CHOP alters the outer mitochondrial membrane stability by downregulating anti-apoptotic proteins (Bcl-2, Bcl-xL) and upregulating pro-apoptotic proteins (Bim, Bax, and Bak) [12]. This triggers cytochrome c release and activates the Caspase-9/3 cascade to induce apoptosis. This precise switch from ATF4-mediated repair to CHOP-mediated cell suicide determines the fate of cancer cells under therapeutic pressure.

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2.3. ATF6 axis: reinforcing proteostasis and stress adaptation

The third canonical branch, ATF6, is activated through a distinct mechanism. Following ER stress, ATF6 translocates from the ER to the Golgi apparatus. Then, it is sequentially cleaved by site-1 and site-2 proteases (S1P, S2P), releasing an active cytosolic transcription factor ATF6-p50. ATF6-p50 induces the expression of ER chaperones, protein-folding enzymes, ERAD components and XBP1, and activates genes governing protein folding, ER quality control and adaptive survival, thereby enhancing the overall adaptive capacity of the ER [13]. Through this transcriptional program, ATF6 reinforces the long-term adaptive capacity of the UPR under persistent ER stress.

Compared with IRE1α and PERK, ATF6 has received relatively less attention in cancer research. Nevertheless, accumulating studies suggest that ATF6 contributes to tumor cell survival under chronic stress and may participate in therapeutic resistance in specific contexts [10, 13]. Its role appears particularly important in maintaining long-term proteostasis when cancer cells are exposed to sustained environmental pressure.

2.4. The functional cooperation among the three branches

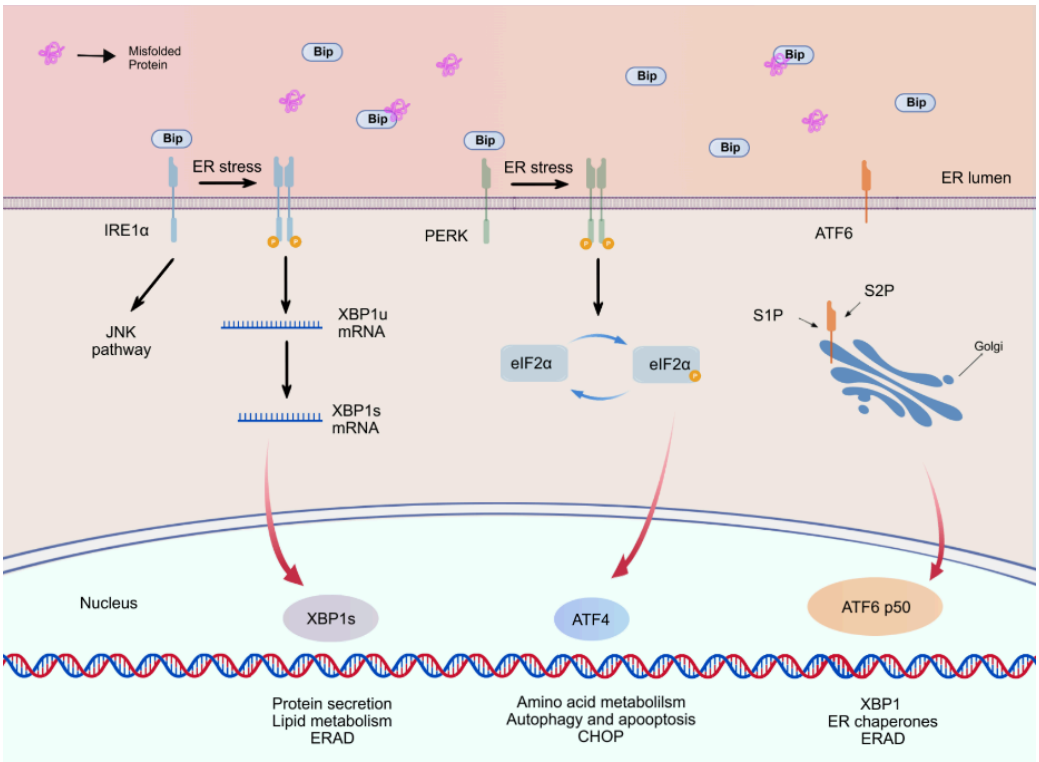


Figure 1. Activation and downstream targets of the three canonical UPR branches. [Misfolded proteins induce ER stress, causing BiP to dissociate and activate three transmembrane sensors: IRE1α, PERK, and ATF6. Specifically, activated IRE1α triggers the c-Jun N-terminal kinase (JNK) pathway and splices XBP1u mRNA into active XBP1s, which enters the nucleus to drive protein secretion, lipid metabolism, and ERAD. PERK phosphorylates eIF2α to selectively induce the transcription factor ATF4, regulating amino acid metabolism, autophagy, and CHOP-mediated apoptosis. ATF6 translocates to the Golgi for cleavage by S1P and S2P proteases, releasing active ATF6-p50 into the nucleus to upregulate the expression of XBP1, ER chaperones, and ERAD. Created with BioGDP]

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Despite some mechanism differences, the three UPR branches ultimately converge to form a coordinated adaptive framework. IRE1α expands the ER folding and secretory machinery, PERK reduces proteotoxic pressure while reshaping cellular metabolism, and ATF6 strengthens ER compensatory capacity through transcriptional reprogramming. Considerable overlap exists among their downstream targets, enabling extensive functional cooperation rather than strict pathway segregation. From a tumor biology perspective, this integration is particularly important because cancer cells rarely seek to eliminate ER stress altogether [14]. Instead, they appear to maintain UPR activity within a narrow adaptive window, where signaling is sufficiently robust to sustain survival and stress tolerance, yet restrained enough to avoid crossing the threshold that initiates apoptosis or other forms of programmed cell death. Such a balance provides the mechanistic basis for the long-term exploitation of UPR signaling during tumor progression (Figure 1).

3. UPR as a survival infrastructure for cancer cells

The primary oncologic function of the UPR after being co-opted by cancer cells is to maintain their survival under conditions that would otherwise lead to proteotoxic collapse and cell death. During tumor progression, cancer cells are continuously exposed to hypoxia, nutrient deprivation, oxidative stress, and excessive protein synthesis driven by oncogenic signaling [2]. Under normal physiological conditions, unresolved stress of this magnitude would force cells to undergo an irreversible transition toward terminal apoptotic programs. In cancer cells, however, the UPR does not operate as a temporary response to acute damage. Instead, it is reprogrammed into a relatively persistent and moderate survival program. By systematically exploiting these stress-management pathways, tumor cells establish an intracellular buffering zone that actively adjusts their survival threshold. This persistent but non-lethal state of UPR activation ensures that cancer cells can maintain viability under metabolic stress, allowing them to adapt to ongoing environmental and metabolic challenges.

3.1. Maintenance of proteastasis

One of the most important survival-promoting functions of UPR is the maintenance of proteostasis. Previous studies have demonstrated that malignant growth is intrinsically coupled to the abnormal expansion of protein translation and secretion, which exposes cancer cells to a substantial risk of proteotoxic collapse [15]. Oncogenic pathways such as myelocytomatosis viral oncogene homolog (MYC), rat sarcoma viral oncogene homolog (RAS), and mechanistic target of rapamycin (mTOR) are highly active in cancer cells, leading to elevated rates of protein synthesis and placing a heavy burden on the protein-folding machinery of the ER [16]. To counteract the accumulation of cytotoxic unfolded protein intermediates, the co-opted UPR activates a comprehensive quality-control network. The IRE1α–XBP1 and ATF6 branches enhance the expression of molecular chaperones, protein-folding enzymes, and components of the ERAD pathway, thereby expanding the protein-folding and secretory capacity of the ER. At the same time, the PERK–eIF2α branch imposes an immediate brake through phosphorylation of eIF2α, resulting in a transient reduction of global protein translation and a decrease in the number of newly synthesized polypeptides entering the stressed ER. Through the coordinated action of these complementary pathways, cancer cells are able to maintain proteostasis even under persistent proteotoxic stress.

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3.2. Metabolic reprogramming

UPR signaling actively rewires cellular metabolism to support survival. Malignant cells do not rely solely on molecular chaperones for adaptation; they also exploit the UPR to reshape their metabolic programs. For example, studies have shown that XBP1 promotes cell survival under hypoxic conditions by reprogramming cellular metabolism. Specifically, XBP1s, generated through the IRE1α pathway, directly interacts with HIF1α to form a transcriptional complex that enhances the expression of genes involved in glycolysis and hypoxic adaptation [8]. Through this mechanism, cancer cells can increase glucose utilization and sustain ATP production under oxygen-limited conditions. In addition, XBP1 contributes to the activation of the hexosamine biosynthetic pathway and lipid biosynthetic pathways, both of which support membrane biogenesis and secretory activity during rapid cell proliferation.

Activation of the PERK branch provides a complementary metabolic adaptation mechanism by ensuring the selective translation of ATF4. ATF4 functions as a central metabolic regulator and controls the expression of genes involved in amino acid uptake, synthesis, and transport. When cancer cells encounter nutrient-limited conditions, the PERK-ATF4 axis promotes amino acid acquisition and biosynthesis, enabling cells to maintain metabolic flexibility despite restricted nutrient availability [17]. Collectively, these findings indicate that the UPR reshapes metabolic pathways to optimize nutrient acquisition and utilization, allowing tumor cells to preserve metabolic integrity and lipid biosynthetic capacity even within harsh and nutrient-poor microenvironments.

3.3. Oxidative stress adaptation and autophagy activation

UPR-mediated adaptation is further reinforced through the buffering of oxidative stress and its interaction with autophagy. Due to mitochondrial dysfunction, oncogene activation, and stresses arising from the tumor microenvironment, ROS are commonly present at high levels in tumor cells [16]. Persistent oxidative damage threatens genomic integrity and cellular survival, making antioxidant defense mechanisms essential for tumor fitness. Experimental studies have shown that PERK deficiency leads to increased oxidative stress and impaired tumor growth [18]. This critical protective response is fundamentally driven by the PERK pathway via the activation of nuclear factor erythroid 2-related factor 2 (NRF2)-dependent antioxidant programs, thereby reducing oxidative DNA damage and limiting the lethal activation of the DNA damage response (DDR). These findings collectively highlight the indispensable role of this signaling axis in maintaining cancer cell adaptation and survival.

ER stress also regulates cell fate through extensive crosstalk with the autophagy pathway. It initiates autophagy through both the PERK–ATF4 and IRE1α–JNK signaling pathways. This process facilitates the clearance of damaged proteins and organelles, thereby alleviating proteotoxic stress. When ER stress exceeds the threshold of reversible adaptation, sustained ATF4 expression induces the expression of key autophagy-related genes, including autophagy-related 5 (ATG5) and microtubule-associated protein 1 light chain 3 (LC3), thereby promoting autophagy [19]. In parallel, activation of the IRE1α branch stimulates the JNK signaling pathway, which phosphorylates Bcl-2 and releases Beclin1 from Bcl-2-mediated inhibition, further facilitating autophagy initiation. Through the coordinated activation of these pathways, cells remove damaged proteins and organelles while recycling intracellular nutrients to maintain cellular homeostasis. Under conditions of severe microenvironmental stress, this cooperative network functions as an important safety valve by balancing intracellular redox homeostasis and clearing proteotoxic debris, thereby enhancing cellular stress tolerance and prolonging cell survival.

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3.4. Oncogenic signaling in UPR

Notably, there is a bidirectional relationship between oncogenic signaling and the UPR. The persistent stress state observed in tumor cells is not merely a passive consequence of microenvironmental damage. Major oncogenic drivers, including MYC, RAS, and hyperactivated mTOR complexes, promote extensive protein synthesis, resulting in an overload of unfolded proteins that can trigger proteotoxic stress and ultimately lead to cell death. To cope with this burden, cells must continuously enhance the capacity of the ER protein-folding machinery in order to relieve proteotoxic pressure. Studies have shown that these oncogenic signals actively engage and sustain UPR activation, making the UPR an essential supporting pathway during malignant progression [15].

Oncogenes can induce ER stress through excessive protein synthesis while simultaneously creating a dependency on adaptive UPR signaling for cellular survival. For example, MYC-driven tumors display a greater dependence on the IRE1α–XBP1 pathway, and pharmacological inhibition of this signaling axis results in marked tumor cell vulnerability. In addition, ATF4 has been shown to couple MYC-dependent translational activity with cellular bioenergetic programs, helping tumor cells meet the increasing metabolic demands associated with rapid proliferation [20]. These findings indicate that UPR is not simply a passive response to oncogenic stress. Rather, it has become integrated into oncogene-driven programs and serves as an essential component of the malignant survival machinery. Therefore, cancer cells do not merely tolerate chronic ER stress; instead, they actively exploit adaptive UPR signaling to establish a stable and sustainable survival state. This survival state subsequently provides the biological foundation for tumor metastasis and therapy resistance.

4. From survival to dissemination: UPR driven metastasis and dormancy

Once cancer cells acquire the ability to survive under conditions of chronic ER stress, UPR signaling can further support their metastatic dissemination to distant organs. The classical "seed and soil" hypothesis proposed by Stephen Paget suggests that tumor metastasis not only depends on the intrinsic properties of tumor cells (the "seed") but also on their compatibility with the microenvironment of distant organs (the "soil") [21]. Therefore, successful metastasis requires not only migratory and invasive capabilities but also the ability of cancer cells to tolerate hostile conditions and survive long enough to locate and adapt to a suitable distant organ.

However, metastasis is an extremely inefficient and highly stressful process. To successfully colonize distant tissues, disseminated tumor cells must withstand multiple severe challenges. During dissemination, tumor cells must detach from the extracellular matrix (ECM), resist oxidative stress within the circulation, survive in an environment lacking familiar growth factors, and eventually establish colonization within distant tissues. These environmental changes increase intracellular ROS accumulation and disrupt protein-folding homeostasis, thereby inducing ER stress. Cancer cells overcome these challenges by exploiting the UPR to establish a persistent but non-lethal adaptive platform, allowing them to maintain viability throughout the metastatic process. This stress-adaptive state provides the biological basis for their successful dissemination and colonization.

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4.1. UPR-mediated anoikis resistance

A major barrier during metastasis is anoikis, a specialized form of apoptosis triggered by the loss of cell adhesion to the ECM. The initial step of metastasis requires cancer cells to detach from the structural ECM of the primary tumor and enter a suspended state. Under normal physiological conditions, cells undergo anoikis following ECM detachment, thereby preventing abnormal colonization at distant sites. However, cancer cells exploit the UPR to acquire resistance to anoikis.

Many studies have demonstrated that the PERK signaling pathway plays a crucial role in this process. Upon detachment from the ECM, PERK-mediated phosphorylation of eIF2α activates ATF4-dependent stress programs, thereby reducing oxidative damage and promoting cell survival under anchorage-independent conditions [22]. In addition, PERK signaling supports antioxidant responses through the activation of NRF2, limiting the accumulation of ROS that would otherwise induce apoptosis. Experimental evidence has further shown that inhibition of PERK or eIF2α signaling impairs the survival of matrix-detached tumor cells and also reduces their ability to promote angiogenesis [23]. Collectively, these findings indicate that PERK signaling is not a direct driver of metastasis itself, but rather provides a critical survival advantage during the early stages of dissemination. By enabling detached cancer cells to evade anoikis, the UPR increases the likelihood of successful metastatic colonization.

4.2. Supporting EMT and invasive plasticity

UPR signaling can also facilitate the acquisition of an invasive phenotype. Epithelial-mesenchymal transition (EMT) is a metastasis-associated process in which cancer cells undergo extensive cytoskeletal remodeling and upregulate the production of ECM-remodeling components, structural integrins, and matrix metalloproteinases. The massive increase in newly synthesized proteins during this transition imposes a substantial secretory burden on the ER network, requiring UPR activation to prevent proteotoxic cell death.

Studies have shown that PERK activation promotes the expression of the metastasis-associated transcription factor cAMP responsive element-binding protein 3-like 1, thereby enhancing ECM remodeling and metastatic dissemination in breast cancer models. In addition, activation of the IRE1α–XBP1 pathway has been associated with EMT-related transcriptional programs and increased invasive potential in multiple types of cancer. For example, overexpression of lysyl oxidase-like 2 leads to its accumulation within the ER, where it interacts with heat shock protein family A member 5. This interaction activates the IRE1α–XBP1 pathway and subsequently upregulates multiple EMT-associated transcription factors, including snail family transcriptional repressor 1 (SNAI1), SNAI2, zinc finger E-box binding homeobox 2, and transcription factor 3, ultimately promoting the initiation and progression of EMT [24]. However, the relationship between UPR signaling and invasion remains highly context dependent. Excessive or prolonged ER stress may cause apoptosis and thus hinder cell migration [2]. Therefore, current evidence supports the view that it is the adaptive UPR, rather than terminal UPR, that primarily promotes invasive ability.

4.3. Maintenance of tumor cell dormancy

When tumor cells reach distant organs or tissues, they do not necessarily begin to proliferate immediately. Many disseminated tumor cells first enter a dormant state, which is generally categorized into tumor mass dormancy and cellular dormancy. During cellular dormancy, cancer cells remain in the G0–G1 phase of the cell cycle, maintaining viability while largely ceasing

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proliferation. These dormant cells have significant clinical importance because they can survive for years and later reactivate to initiate disease recurrence.

Accumulating evidence suggests that dormant tumor cells maintain a persistent stress-adaptive program that is highly dependent on UPR signaling. Elevated expression of stress-associated proteins, including BiP/GRP78, GRP94, PERK, and ATF6, has been repeatedly observed in dormant cancer cells. UPR induces G1 cell cycle arrest through activation of the PERK–eIF2α pathway, which suppresses the translation of cyclin D1. Importantly, even in the absence of PERK, this process can be maintained through alternative eIF2α kinases such as general control nonderepressible 2, indicating that eIF2α phosphorylation-mediated translational suppression is supported by a redundant and robust regulatory network. In addition, studies have shown that unresolved ER stress can promote the survival of latent pancreatic metastatic cells through activation of adaptive UPR signaling [25]. These findings suggest that dormancy is not simply a passive quiescent state. Instead, it represents an active survival strategy in which cancer cells maintain proteostasis and metabolic homeostasis by dynamically regulating protein translation and cell cycle progression under unfavorable microenvironmental conditions. Notably, dormant cells generally exhibit reduced sensitivity to chemotherapy. Therefore, the ability of UPR signaling to maintain the survival of dormant tumor cells may contribute to therapeutic failure and disease recurrence, further linking the role of adaptive UPR in tumor dormancy with its function in therapy resistance.

5. UPR as a driver of therapy resistance

Under therapeutic stress, persistent but non-lethal UPR activation no longer acts as a temporary repair response. Instead, it establishes a stress-adaptive state that enables cancer cells to survive therapeutic pressure and avoid cell death [26]. This adaptive state mainly contributes to resistance to chemotherapy and immunotherapy.

5.1. UPR-mediated resistance to chemotherapy

An important mechanism by which the UPR promotes chemotherapy resistance is the reduction of intracellular drug accumulation. Studies have shown that UPR signaling upregulates ATP-binding cassette (ABC) transporters responsible for drug efflux, including multidrug resistance protein 1, thereby actively pumping chemotherapeutic agents out of the cytoplasm [27]. This minimizes intracellular drug accumulation and helps maintain cancer cell viability. In addition to regulating drug disposition, UPR signaling also enhances cellular tolerance to genotoxic therapy by modulating the DDR. It has been reported that XBP1s upregulates the transcription of DDR-related genes in human hepatocytes, thereby increasing drug resistance [27]. Furthermore, PERK signaling maintains cellular redox homeostasis through activation of NRF2-dependent antioxidant pathways, which support the DDR. ATF4 has also been shown to increase the expression of cleavable topoisomerase complexes. Together, these mechanisms protect tumor DNA from damage induced by chemotherapeutic agents such as cisplatin, thereby promoting cancer cell survival.

Another important feature of UPR-mediated chemotherapy resistance is the establishment of tolerance to therapy-induced cell death. UPR signaling cooperates extensively with the autophagy pathway. Activation of the PERK–ATF4 axis induces the expression of autophagy-related genes, including ATG5, allowing cancer cells to remove damaged proteins and organelles while recycling intracellular nutrients under therapeutic stress. As discussed earlier, PERK-mediated reduction of ROS also decreases the sensitivity of cancer cells to cell death. Together, these coordinated stress

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responses enhance cellular adaptation, reduce the intracellular accumulation and cytotoxic effects of anticancer drugs, and ultimately promote therapy resistance.

5.2. UPR-mediated resistance to immunotherapy

Immunotherapy has become an important strategy for cancer treatment by harnessing the body's immune system to eliminate tumor cells [28]. However, accumulating evidence indicates that UPR signaling also contributes to resistance to immunotherapy [29]. Persistent UPR activation reshapes the tumor immune microenvironment. Chronic ER stress impairs antigen presentation and drives tumor-associated myeloid cells toward an immunosuppressive phenotype, thereby limiting effective anti-tumor immune responses. In addition, activation of the IRE1α–XBP1 pathway in tumor-infiltrating immune cells disrupts their metabolic homeostasis and weakens their ability to support cytotoxic T-cell function. In ovarian cancer, this pathway also suppresses T-cell infiltration and the expression of interferon-γ. Furthermore, studies have shown that deletion of CHOP in T cells enhances the anti-tumor activity of CD8+ T cells. This finding suggests that the PERK–eIF2α pathway also regulates T-cell function. Collectively, persistent UPR activation impairs T-cell recruitment, promotes T-cell dysfunction, and facilitates immune evasion.

Alterations in the tumor immune microenvironment also impair antigen presentation. UPR signaling suppresses the function of several types of antigen-presenting cells (APCs), including conventional dendritic cells and macrophages. As a result, APCs cannot be efficiently activated to initiate T-cell immune responses, preventing effective recognition and elimination of tumor cells [29]. Notably, UPR signaling also contributes to the maintenance of cancer stemness. Similar to normal stem cells, cancer stem cells (CSCs) possess the capacity for self-renewal and continuous differentiation, and they suppress T-cell activity, thereby promoting resistance to immunotherapy. Studies have shown that the PERK–eIF2α pathway upregulates pluripotency regulators, which increases the CSC population and further enhances immune resistance [30]. Taken together, these findings suggest that therapy resistance shares common mechanisms with tumor survival and metastasis. All three represent different manifestations of the adaptive network established by chronic but non-lethal UPR activation. Therefore, UPR-mediated therapy resistance should be viewed as a broader consequence of cancer cell adaptation during tumor progression, rather than an isolated mechanism responsible for treatment failure.

6. Conclusion and future perspectives

In summary, the UPR is a protective mechanism activated in response to ER stress. Cancer cells exploit this mechanism to adapt to hostile environments, thereby promoting tumor progression and metastasis. This review summarizes the three canonical UPR branches and explains how they cooperate at the mechanistic level to enable cancer cells to tolerate chronic proteotoxic stress and evade cell death. By coordinately regulating proteostasis, metabolic reprogramming, oxidative stress buffering, and autophagy, the UPR provides the fundamental survival capacity required for malignant progression. This adaptive program not only sustains cancer cell survival but also supports tumor metastasis by promoting anoikis resistance and tumor dormancy. Under therapeutic stress, the same stress-adaptive mechanisms are further exploited to promote resistance to chemotherapy and immunotherapy. Based on the current evidence, cancer cell survival, metastasis, and therapy resistance should not be regarded as independent outcomes of UPR activation. Rather, they represent different manifestations of a unified survival strategy established by chronic but non-lethal ER stress at different stages of tumor progression.

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Although considerable progress has been made, many important questions remain unanswered. The biological outcomes of UPR activation are highly dependent on the cellular context, the intensity of stress, and the duration of signaling; however, the molecular mechanisms that determine the switch between adaptive and terminal UPR are still not fully understood [2]. In addition, the major functions of the UPR at different stages of tumor progression have been identified, but further investigation is still needed, particularly regarding the role of UPR in metastatic dormancy. Future studies include the following directions. First, identifying tumor-specific UPR dependencies and clarifying the regulatory mechanisms that govern the switch between adaptive and pro-death UPR signaling. Second, leveraging recent technological advances, such as single-cell sequencing and spatial transcriptomics, to investigate the heterogeneity of ER stress responses within tumors and the mechanisms of intercellular communication, which may help discover key regulatory nodes like BiP. Third, developing combination strategies that integrate UPR-targeted therapy with immunotherapy and precision medicine, as well as multi-drug therapies and Traditional Chinese Medicine, to enhance treatment efficacy and overcome resistance. A major challenge that must be addressed concurrently is the potential toxicity and limited treatment selectivity associated with targeting UPR components, given their broad and essential physiological functions in normal tissues. Through these efforts, the UPR may ultimately be transformed from a hallmark of tumor adaptation into a clinically actionable therapeutic vulnerability.

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