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THE ROLE OF THE INTEGRATED STRESS RESPONSE IN BREAST CANCER THERAPY RESISTANCE

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INTRODUCTION

Breast cancer (BC) is a highly heterogeneous and complex malignancy, comprising biologically and clinically distinct subtypes defined by the immunohistochemical (IHC) expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), along with distinct molecular features (PEROU *et al*., 2000).

Therapeutic resistance remains a fundamental barrier to effective breast cancer treatment, driving disease recurrence, metastatic progression, and mortality. Emerging evidence indicates that resistance is not solely driven by genetic alterations but instead reflects a dynamic process of stress-adaptive cellular reprogramming (MARINE *et al*., 2020).

In this context, the integrated stress response (ISR) has emerged as a central signaling hub that coordinates cellular adaptation to therapeutic and microenvironmental stress across distinct breast cancer subtypes. By coupling translational control to selective transcriptional outputs—primarily through eIF2α phosphorylation and ATF4 activation—the ISR orchestrates adaptive programs that regulate proteostasis, redox balance, and metabolic homeostasis (PAKOS-ZEBRUCKA *et al.*, 2016).

In breast cancer for exemple, ISR activation has been linked to enhanced survival under amino acid deprivation and other metabolic constraints, partly through the induction of stress-responsive non-coding RNAs and metabolic regulators that support tumor cell fitness (WU *et al.*, 2022). Moreover, ISR signaling has been increasingly implicated in the establishment of drug-tolerant cellular states, including phenotypically plastic and persister populations that sustain tumor survival under therapeutic pressure and contribute to relapse and metastatic dissemination (JEWER *et al.*, 2020). These findings position the ISR as a key integrator of stress adaptation in breast cancer, bridging environmental pressures and cellular survival programs that ultimately fuel therapeutic resistance.

This review examines the roles of the ISR in metabolic regulation, proteostasis, tumor plasticity, and responses to anticancer therapies in breast cancer, with a particular focus on how ISR signaling shapes therapeutic outcomes through its context-dependent ability to promote either adaptive survival or stress-induced cell death.

METHODOLOGY

This narrative review was conducted through a structured search of the PubMed database to identify relevant studies on the integrated stress response in breast cancer. The search strategy was based on combinations of keywords and controlled terms using Boolean operators, including (“integrated stress response”) AND (“breast cancer”) AND (“therapy resistance. No time restrictions were applied in order to maximize the scope of retrieved studies. Articles were selected based on their relevance to the molecular mechanisms of ISR signaling and its role in tumor progression and therapeutic response. Recent studies and high-impact publications were considered, as well as seminal reports that established key concepts in the field. Reference lists of selected articles were also screened to identify additional relevant studies. Only articles published in English were included.

RESULTS AND DISCUSSION

The Integrated Stress Response

The integrated stress response (ISR) is an evolutionarily conserved signaling network that functions as a central integrator of cellular

stress, enabling adaptation to diverse intrinsic and extrinsic perturbations, including nutrient deprivation, hypoxia, endoplasmic reticulum (ER) stress, oxidative stress, and viral infection (RYOO & VASUDEVAN, 2017;PAKOS-ZEBRUCKA *et al*., 2016).

At its core, the ISR converges on the phosphorylation of the α-subunit of eukaryotic initiation factor 2 (eIF2α) by a family of stress-responsive kinases—PERK, GCN2, PKR, and HRI—each activated by distinct upstream signals yet collectively eliciting a unified adaptive response. PERK is primarily engaged by ER proteotoxic stress, GCN2 senses amino acid deprivation through uncharged tRNAs, PKR is activated by double-stranded RNA during viral infection, and HRI responds to heme deficiency and redox imbalance. This modular architecture enables the ISR to integrate diverse stress inputs into a coordinated signaling output (RYOO & VASUDEVAN, 2017; PAKOS-ZEBRUCKA *et al*., 2016).

Phosphorylation of eIF2α imposes a rapid and global attenuation of cap-dependent translation, thereby alleviating proteostatic burden and conserving metabolic resources. This translational repression is coupled to the selective translation of a subset of mRNAs, most prominently activating transcription factor 4 (ATF4), ATF5 and CHOP (PAKOS-ZEBRUCKA *et al.*, 2016). ATF4 orchestrates a transcriptional program that promotes cellular adaptation by regulating amino acid metabolismo (AVEROUS *et al.*, 2004); redox homeostasis (HARDING *et al.*, 2003); autophagy and survival (B'CHIR *et al*., 2013).

Importantly, ISR signaling also incorporates intrinsic feedback regulation. Induction of GADD34 promotes eIF2α dephosphorylation, restoring translational activity and limiting excessive stress signaling (PAKOS-ZEBRUCKA *et al.*, 2016). However, under conditions of sustained or unresolved stress, ATF4 cooperates with CHOP to drive a transcriptional shift toward apoptosis, thereby linking ISR activation to cell fate determination (PAKOS-ZEBRUCKA *et al.*, 2016).

Beyond the canonical eIF2α–ATF4 axis, the ISR is closely interconnected with the mechanistic target of rapamycin complex 1 (mTORC1), establishing a complementary regulatory arm that strengthens translational control (RYOO & VASUDEVAN, 2017). Stress conditions that activate ISR kinases frequently converge on the suppression of mTORC1 activity through multiple mechanisms, including activation of energy-sensing pathways (such as AMPK), nutrient-sensing circuits downstream of GCN2, or stress-induced signaling cascades associated with ER dysfunction (RYOO & VASUDEVAN, 2017). Inhibition of mTORC1 results in the dephosphorylation and activation of eukaryotic initiation factor 4E-binding protein 1 (4EBP1), which sequesters eIF4E and thereby suppresses cap-dependent translation initiation. This mechanism acts in concert with eIF2α phosphorylation to impose a second translational regulation step, while selectively preserving the translation of stress-adaptive transcripts (RYOO & VASUDEVAN, 2017).

Collectively, the ISR operates as a multilayered regulatory system that integrates translational and transcriptional control to reprogram cellular function under stress. Crucially, the outcome of ISR activation is highly context-dependent: transient activation promotes adaptation and recovery, whereas sustained signaling can trigger apoptotic programs.

The Integrated Stress Response in breast cancer: molecular mechanisms driving tumor progression and adaptation

In breast cancer, accumulating evidence indicates that ISR activation contributes to multiple hallmarks of tumor progression, in-

cluding metabolic rewiring, proteostasis maintenance, cellular plasticity, and therapy resistance. ATF4 coordinates transcriptional programs that reshape metabolic pathways, redox balance, autophagy, and cell fate decisions. However, the functional consequences of ISR activation in breast cancer are highly context-dependent and vary across tumor subtypes and stress conditions. In this section we describe the mechanisms by wich the ISR promote breast cancer progression

Metabolic reprogramming and redox homeostasis

Metabolic adaptation represents a central output of ISR signaling in breast cancer, enabling tumor cells to dynamically adjust nutrient utilization and maintain redox balance under fluctuating microenvironmental conditions. Rather than acting as a passive response to stress, ISR-driven metabolic reprogramming actively supports tumor progression and metastatic competence.

A key component of this adaptation is the regulation of redox homeostasis. Recent evidence demonstrates that mitochondrial glutathione import is required for metastatic dissemination through sustained ISR activation, highlighting a functional link between redox buffering capacity and stress signaling (YEH *et al.*, 2025). Enhanced mitochondrial glutathione availability not only protects against oxidative damage but also maintains ISR activity, promoting metastatic competence (YEH *et al.*, 2025).

In parallel, amino acid sensing through GCN2 activation plays a pivotal role in metabolic adaptation. Under conditions of nutrient deprivation, GCN2–eIF2α–ATF4 signaling induces transcriptional programs that support amino acid homeostasis and survival. For instance, the long non-coding RNA UBA6-AS1 is upregulated in response to arginine or glutamine deprivation in triple-negative breast cancer (TNBC), promoting tumor cell survival both in vitro and in vivo and underscoring the importance of ISR-dependent transcriptional regulation in metabolic stress during tumor progression (WU *et al.*, 2022).

Notably, ISR activation can also occur through noncanonical pathways. Methionine restriction, for example, triggers ISR signaling independently of GCN2 and PERK, highlighting the diversity of upstream inputs that converge on this pathway in breast cancer (RAJANALA *et al*., 2019). Furthermore, ISR signaling modulates nutrient utilization in a context-dependent manner. Under glucose deprivation, induction of a mitochondrial isoform of the glutamine transporter SLC1A5 (SLC1A 5var) increases glucose dependency in TNBC cells, reprograms metabolic fluxes and enhances cellular vulnerability to metabolic stress (WANG *et al*., 2024), illustrating that ISR-driven metabolic outputs can either promote survival or sensitize cells to stress depending on context.

Collectively, these findings establish ISR signaling as a key regulator of metabolic plasticity in breast cancer, coordinating nutrient sensing, redox control, and mitochondrial function to shape tumor cell fitness under stress.

ISR and proteostasis control

Proteostasis—the dynamic balance between protein synthesis, folding, and degradation—is essential for cellular homeostasis and is frequently challenged in cancer cells due to elevated protein synthesis rates and oncogenic stress. ISR signaling is a critical component of the proteostasis network, coupling translational attenuation with adaptive responses that mitigate proteotoxic stress.

Upon disruption of protein folding capacity, ISR activation reduces global protein synthesis while selectively inducing transcriptional pro-

grams that enhance protein quality control and degradation pathways. This coordinated response enables cancer cells to buffer the accumulation of misfolded or damaged proteins and sustain viability under stress conditions (WANG & KAUFMAN, 2014).

Importantly, the contribution of ISR signaling to proteostasis is highly context-dependent. In models of luminal and triple-negative breast cancer, distinct ISR kinases have been shown to differentially regulate cellular responses to proteotoxic stress (SANNINO *et al.*, 2021). Inhibition of the molecular chaperone Hsp70, for example, reveals a functional divergence in ISR signaling: PERK activation predominantly drives pro-apoptotic responses in sensitive cells, whereas GCN2 promotes autophagy-mediated survival in resistant populations (SANNINO *et al.*, 2021). These findings highlight the modular nature of ISR signaling and its differential integration within proteostasis networks in breast cancer cells (SANNINO *et al.*, 2021).

Thus, ISR signaling not only preserves proteome integrity but also contributes to cell fate decisions by balancing adaptive and apoptotic responses to proteotoxic stress.

ISR in metastasis and cellular plasticity

In addition to maintaining metabolic and proteostatic homeostasis, ISR signaling also influences cellular identity and behavior, thereby contributing to phenotypic plasticity and tumor dissemination.

ISR signaling is increasingly recognized as a key regulator of breast cancer metastasis and cellular plasticity. By modulating translational and transcriptional programs, the ISR enables tumor cells to dynamically transition between phenotypic states, facilitating adaptation to changing microenvironments during tumor progression and dissemination.

Activation of the GCN2–eIF2α–ATF4 axis has been directly implicated in metastatic progression. ETHE1-mediated activation of this pathway enhances eIF2α phosphorylation and promotes ATF4-dependent transcriptional programs that drive migration, invasion, and metastatic colonization in triple-negative breast cancer models (YANG *et al.*, 2023). Mechanistically, ETHE1 facilitates the interaction between GCN2 and eIF2α, thereby amplifying ISR signaling and promoting expression of genes associated with cell motility and metastasis (YANG *et al*., 2023).

Beyond transcriptional regulation, ISR-dependent translational reprogramming plays a critical role in cellular plasticity. Selective translation of mRNA isoforms encoding key regulators of stemness and epithelial–mesenchymal transition (EMT), including NANOG, SNAIL, and NODAL, promotes the emergence of stem cell–like phenotypes that are associated with increased tumor-initiating capacity and resistance to therapy (JEWER *et al.*, 2020).

Interestingly, both activation and attenuation of ISR signaling can support metastatic potential, depending on the cellular context. Overexpression of eIF2Bδ in breast cancer stem cells dampens ISR signaling by counteracting eIF2α phosphorylation, thereby preventing excessive stress responses while maintaining translational capacity required for stem cell maintenance and metastasis (GUPTA *et al.*, 2023). This highlights the importance of finely tuned ISR activity in regulating tumor cell fitness.

Furthermore, microenvironmental stressors such as hypoxia can induce ATF4-dependent survival programs that enable detached tumor cells to resist anoikis and survive during metastatic dissemination, reinforcing the role of ISR signaling in metastatic competence (KIESEL *et al.*, 2022; HSU *et al*., 2022).

ISR and quiescence

ISR signaling plays a critical role in maintaining quiescent and slow-cycling tumor cell populations, including disseminated cancer cells (DCCs), which evade conventional therapies. In HER2+ models, dormant cells exhibit high ISR activity, and pharmacological inhibition of PERK selectively eliminates these cells and blocked metastasis (CALVO *et al.*, 2023). Importantly, treatment with CDK4/6 inhibitors (to force a quiescent state) followed by inhibition of PERK further reduced metastatic burden (CALVO *et al.*, 2023).

ISR in therapeutic resistance

The ISR contributes to resistance across multiple therapeutic modalities by enabling tumor cells to adapt to treatment-induced stress. Through coordinated translational and metabolic reprogramming, ISR signaling supports survival under cytotoxic, oxidative, and metabolic challenges imposed by anticancer therapies.

Chemotherapy

Activation of ISR signaling has been implicated in resistance to chemotherapeutic agents such as paclitaxel. Paclitaxel-induced activation of the PERK/EIF2AK4–eIF2α–ATF4 axis promotes the expression of the major antioxidant enzymes HMOX1, SHMT2, and SLC7A11, which maintain redox homeostasis and limit therapy-induced oxidative damage (CHEN *et al.*, 2019). Disruption of ISR signaling or ATF4 expression sensitizes tumor cells to paclitaxel, underscoring its protective role.

Similarly, polyploid cancer cells that survive cisplatin treatment exhibit sustained ISR activation, supporting a stress-adapted state associated with cancer cell persistence (GONYE *et al.*, 2026).

Radiotherapy

Constitutive activation of the eIF2α–ATF4 axis represents a key determinant of radioresistance in triple-negative breast cancer (TNBC) cells. This pathway promotes glutathione biosynthesis through the induction of genes such as *GCLC*, *SLC7A11*, and *CTH*, thereby increasing intracellular levels of reduced glutathione (GSH), enhancing antioxidant capacity, and limiting the accumulation of reactive oxygen species (ROS) following irradiation, ultimately leading to a radioresistant phenotype (BAI *et al.*, 2021). Inhibition of eIF2α phosphorylation exacerbates oxidative stress by disrupting ATF4-mediated GSH biosynthesis and sensitizes tumor cells to radiation both in vitro and in vivo (BAI *et al.*, 2021). Notably, this signaling cascade is significantly upregulated in human TNBC tissues and is associated with poor patient outcomes (BAI *et al.*, 2021).

Endocrine therapy

Endocrine therapies such as tamoxifen impose selective pressure that promotes ISR activation in NF-κB^{+}/ER-positive breast cancer cell subpopulations (SEMINA *et al.*, 2022).

ISR signaling supports survival and regrowth of these cells following treatment withdrawal, contributing to tumor recurrence (SEMINA *et al.*, 2022).

In addition, oncogenic gene fusions such as KAT6B::ADK, which enhances ADK kinase activity, activate the GCN2–eIF2α–ATF4 axis, thereby driving metastatic potential and endocrine resistance (OU-YANG *et al.*, 2025). Both ATF4 knockdown and GCN2 inhibition reversed tamoxifen resistance, establishing the ISR pathway as the mechanistic link between KAT6B::ADK and endocrine therapy resistance (OU-YANG *et al.*, 2025).

Targeted therapies

In the context of targeted therapies, ISR signaling exerts highly context-dependent ef-

fects, functioning either as a mediator of therapeutic efficacy or as a mechanism of resistance.

In HER2-positive breast cancer, activation of the PKR–eIF2α axis can exert an antitumor function, as it is selectively induced by trastuzumab in treatment-sensitive tumors but not in resistant counterparts (DARINI *et al.*, 2019). This antitumor effect is mediated by ATF4, which upregulates the CDK inhibitor p21^CIP1 and activates JNK1/2 signaling, thereby promoting growth inhibition and stress-induced cytotoxic responses. Consistently, pharmacological stimulation of eIF2α phosphorylation enhances trastuzumab efficacy in resistant HE R2-positive tumors and is associated with improved clinical responses in patients with metastatic disease, indicating that therapeutic activation of ISR signaling can restore drug sensitivity (DARINI *et al.*, 2019).

In contrast, proper activation of the ISR signaling might instead support resistance to the transcriptional CDK7 inhibitor THZ1. Basal breast cancer cell lines, including BT549 and MDA-MB-231, that failed to activate a complete ISR program, exhibit increased sensitivity to THZ1 compared with their luminal counterparts, suggesting that ISR competence represents a determinant of therapeutic response in this contexto (KARTHA *et al.*, 2023). Besides, ISR activation—characterized by increased phosphorylation of eIF2α, upregulation of AT F4, and reduced p4EBP1 levels—can be induced by pharmacological mTOR inhibitors in hormone receptor positive and TNBC cells, driving the emergence of stem cell–like phenotypes associated with therapeutic resistance (JEWER *et al.*, 2020). While inhibition of ISR reduces cellular plasticity and limits tumor progression (JEWER *et al.*, 2020)

Together, these findings highlight the dual and context-dependent role of ISR signaling in targeted therapy, where its activation may either potentiate antitumor responses or sustain adaptive resistance depending on tumor subtype and therapeutic mechanism.

Immunotherapies

Within the tumor microenvironment, chronic activation of ATF4 imposed by hypoxia in $CD8^+$ T lymphocytes, induces metabolic polarity (characterized by hyperactive mitochondrial activity), mitochondrial oxidative stress, and apoptosis, thereby compromising the antitumor immune response (ALICEA PAUNETO *et al.*, 2025). This dysfunction contributes to resistance to immunotherapies, such as immune checkpoint inhibitors, positioning the ISR as a key regulator of immune evasion (ALICEA PAUNETO *et al.*, 2025).

Emerging therapies

Beyond its role in shaping responses to conventional and targeted therapies, ISR signaling also represents a tractable therapeutic vulnerability that can be pharmacologically exploited.

Pharmacological agents such as ONC201, a first-in-class imipridone currently in clinical trials for the treatment of multiple cancers, activate the ISR to induce mitochondrial and metabolic reprogramming—including inhibition of oxidative phosphorylation and increased lactate production—thereby suppressing the proliferation of breast cancer cells (GRAVES *et al.*, 2019). Mechanistically, ONC201 activates the ATP-dependent ClpP protease, a mitochondrial quality control protease linked to the mitochondrial unfolded protein response (mtU PR), promoting the degradation of mitochondrial proteins. The resulting peptide fragments are exported from mitochondria and trigger ISR activation, increasing ATF4 and CHOP, leading to reduced activity of key mitochondrial proteins such as TFAM and TUFM and inhibition of global protein synthesis, ultimately

culminating in metabolic reprogramming and cytostatic phenotype in TNBC cells (GRAVES *et al.*, 2019).

Furthermore, sustained ISR activation following prolonged exposure (>48 h) to ONC201 in HER2-positive breast cancer cells is associated with an irreversible transition to a senescent state, characterized by cell cycle arrest, suppression of proliferation, and inhibition of the intrinsic apoptotic pathway. rast, short-term exposure induces reversible adaptations, underscoring a time-dependent cellular response (MISHUKOV *et al.*, 2022).

CONCLUSION

The integrated stress response (ISR) emerges as a central regulator of breast cancer biology, coordinating translational control, metabolic adaptation, proteostasis, and cellular plasticity. Through these mechanisms, ISR signaling enables tumor cells to dynamically respond to microenvironmental and therapeutic stress.

Importantly, the functional outcome of ISR activation is highly context-dependent, with the capacity to promote either tumor cell survival and therapy resistance or stress-induced cell death. This duality highlights the ISR as both a driver of tumor adaptation and a potential therapeutic vulnerability.

Future therapeutic strategies will require precise modulation of ISR signaling, taking into account tumor subtype, stress context, and treatment modality. Targeting this pathway may offer new opportunities to overcome therapeutic resistance and improve clinical outcomes in patients with breast cancer.

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