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REVIEW

# Current Knowledge of the Integrated Stress Response in the Development and Management of Acute Myeloid Leukemia: A Novel Target with Encouraging Progress

Wanzhi Jiang[1,2,*], Yaonan Hong[1,2,*], Peicheng Wang[1,2,*], Xiawan Yang[1–3], Keding Shao[4], Man Li[1,5], Dijiong Wu[1–3,6]

[1]Department of Hematology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, Zhejiang, People's Republic of China; [2]The First School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, People's Republic of China; [3]National Traditional Chinese Medicine Clinical Research Base (Hematology), Hangzhou, Zhejiang, People's Republic of China; [4]Office of Academic Research, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [5]Department of Pharmacy, The First Hospital of Jiaxing & First Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang, People's Republic of China; [6]Department of Oncology and Hematology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Zhejiang Chinese Medicine University, Wenzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dijiong Wu, Department of Hematology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310006, People's Republic of China, Tel +86-0571-86620325, Email wudijiong@zcmu.edu.cn; Man Li, Department of Pharmacy, The First Hospital of Jiaxing & First Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang, 314000, People's Republic of China, Email liman1451098759@163.com



**Abstract:** Primary or acquired resistance to standard chemotherapy and novel targeted therapies remains a common cause of relapsed/refractory acute myeloid leukemia (AML). The five-year overall survival rate for AML patients remains poor. Exploring novel therapeutic pathways may offer effective strategies to address this challenge. The Integrated Stress Response (ISR) is a signaling pathway that maintains cellular homeostasis by reducing global protein synthesis in response to external and internal stressors. Recent studies have demonstrated that ISR exerts a dual role in AML. Moderate activation of ISR supports hematopoietic and leukemia stem cell maintenance and promotes AML progression, whereas hyperactivation of ISR induces apoptosis and reduces myeloid cell leukemia-1 (MCL-1) expression. MCL-1 overexpression contributes to venetoclax resistance. However, MCL-1 inhibitors have shown disappointing cardiac toxicity in clinical studies. Hyperactivation of the ISR can indirectly suppress MCL-1 and help reverse venetoclax (ABT-199) resistance, as reported in previous studies. Our previous study also indicates that ISR activation can reverse venetoclax resistance in AML cells. These findings support the ISR as a novel therapeutic target in AML. However, the mechanisms by which ISR influences stemness and resistance are not yet fully understood. This review integrates current mechanistic insights and preclinical evidence to highlight the ISR as both a key driver of leukemogenesis and a promising target for overcoming drug resistance in AML. We searched the literature up to October 2025 in PubMed, Google Scholar, and ClinicalTrials.gov using terms related to AML, ISR signaling, venetoclax, and ISR kinases.

**Keywords:** acute myeloid leukemia, integrated stress response, eIF2α, ATF4, resistance

## Introduction

Acute myeloid leukemia (AML) is a highly heterogeneous hematologic malignancy characterized by the clonal proliferation of immature and functionally impaired hematopoietic cells.[1] The standard treatment for AML includes intensive chemotherapy with cytarabine plus an anthracycline (the 7+3 regimen) and stem cell transplantation. Approximately 60–80% of younger patients (age < 60 years) achieve initial remission with the 7+3 regimen.[2] However, elderly patients and younger patients with comorbidities often do not benefit from this approach.

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Advances in the understanding of AML pathophysiology have led to the development of novel targeted therapies, including BCL-2 inhibitors, FLT3 inhibitors, IDH1/2 inhibitors, and p53 reactivators.[3] Among these, venetoclax (ABT-199), is a BCL-2 inhibitor that has shown significant clinical potential in recent years. Despite this progress, a retrospective study reported that 41 (43%) AML patients failed to respond to frontline hypomethylating agents (HMAs) combined with venetoclax and exhibited poor outcomes despite salvage treatment.[4] In addition, acquired loss-of-function mutations in the BAX gene have been identified in 17% of AML patients who relapsed after venetoclax-based therapy, directly contributing to the development of venetoclax resistance.[5] This underscores the urgent need to explore novel therapeutic strategies to overcome venetoclax resistance.

The Integrated Stress Response (ISR) is a conserved signaling network in eukaryotic cells that attenuates global protein synthesis to maintain cellular homeostasis under various stress conditions. Emerging evidence indicates a potential role for the ISR in leukemogenesis and therapeutic resistance.[6] Our previous research also demonstrated that usnic acid, a component of traditional Chinese medicine, can activate the ISR pathway and synergize with the BCL-2 inhibitor venetoclax to enhance chemosensitivity in AML cells.[7] Meanwhile, experimental evidence published in Blood and another study suggest that the ability of gilteritinib to overcome BCL-2 inhibitor resistance in FLT3-negative refractory AML may also be associated with ISR.[8,9] Therefore, this review aims to elucidate the mechanisms by which the ISR contributes to AML progression and proposes its potential as a therapeutic target in AML.

## The Biology of ISR: Functions and Components

ISR senses and integrates a wide array of intrinsic and extrinsic stress signals, regulating the eukaryotic initiation factor 2 (eIF2) phosphorylation to coordinate protein translation and gene expression, thereby facilitating cellular adaptation to environmental fluctuations.[10]

EIF2 is a GTP-binding protein composed of three subunits: α, β, and γ, and it plays a pivotal role in regulating protein synthesis in eukaryotic cells. The α-subunit of eIF2 (eIF2α) is the central mediator of the ISR and serves as the primary phosphorylation target of the four kinases involved in this pathway (Figure 1). Four kinases of eIF2α activate ISR: General Control Nonderepressible 2 (GCN2), Protein Kinase R (PKR), Heme-Regulated Inhibitor (HRI), and PKR-like Endoplasmic Reticulum Kinase (PERK). These kinases respond to various stressors such as endoplasmic reticulum (ER) stress, amino acid deprivation, heme deficiency, double-stranded RNA viruses, and mitochondrial dysfunction.[11–14]

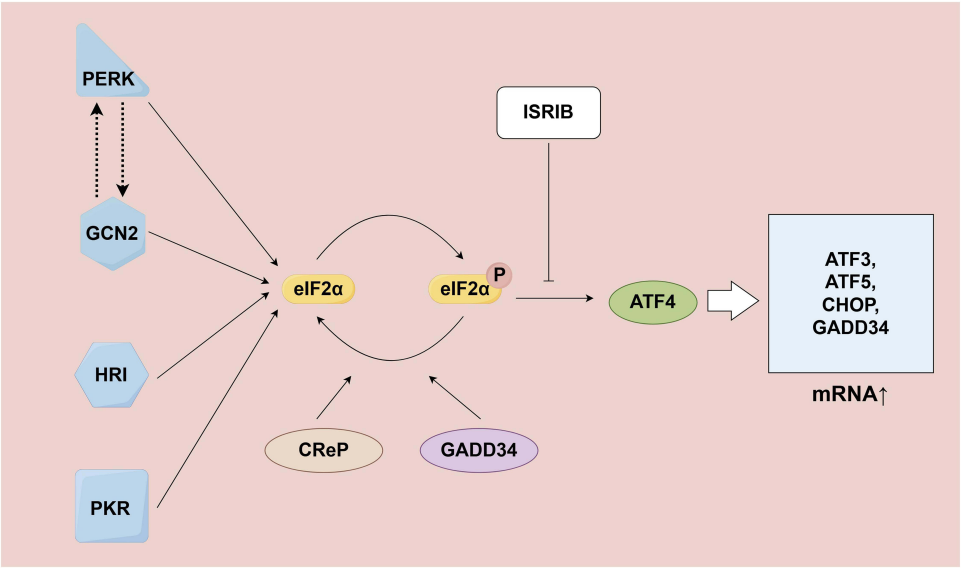


**Figure 1** ISR pathway components. Four stress-responsive kinases initiate the ISR. PERK is activated by ER stress; GCN2 by amino-acid deprivation; HRI by heme or mitochondrial stress; and PKR by double-stranded RNA. These kinases phosphorylate eIF2α and induce ATF4-dependent transcription of ATF3, ATF5, CHOP (DDIT3), and GADD34 (PPP1R15A). CReP and GADD34 mediate negative feedback, while ISRIB functions as a pharmacological inhibitor. Arrows denote activation; dashed arrows denote compensatory interactions; upward arrows denote increased expression or translation; blunt-end lines denote inhibition.

Furthermore, crosstalk between eIF2α kinases enables adaptive signaling compensation, whereby the inhibition or inactivation of one kinase may trigger the activation of another, thereby promoting cell survival. Szaruga M et al[15] reported that PERK inhibitors not only suppress PERK activity but also activate GCN2 at micromolar concentrations. Similarly, another study demonstrated that high concentrations of PERK inhibitors induced GCN2 activation in pancreatic cancer cells,[16] indicating a compensatory rerouting of the ISR upon kinase inhibition.

These kinases phosphorylate eIF2α at serine 51, leading to the selective translation of stress-related mRNAs.[17] Key targets include activating transcription factor 4 (ATF4), ATF5, C/EBP Homologous Protein (CHOP, also named as DDIT3), and GADD34 (also named as PPP1R15A).[18] Among these, ATF4 is the primary transcript and serves as the principal regulator within the ISR. Phosphorylation of eIF2α (p-eIF2α) facilitates ATF4 translation, which in turn activates downstream signaling cascades and transcriptional programs that determine whether the cell adapts or undergoes apoptosis.[19,20] Meanwhile The ISR is modulated by two negative feedback regulators, GADD34 and CReP, which tightly control the amplitude and duration of ISR activation.[21] Additionally, Integrated Stress Response Inhibitor (ISRIB), a small-molecule pharmacological inhibitor, counteracts the translational repression induced by p-eIF2α.

## Exploring ISR as a Novel Target in AML Pathogenesis and Therapeutic Sensitization

The ISR functions as a global modulator of protein synthesis, allowing cells to cope with internal and external stress. The development and progression of AML are driven by several pathological factors, including the abnormal proliferation of hematopoietic stem cells (HSCs), the survival of leukemia stem cells (LSCs), genetic mutations, and a dysregulated bone marrow microenvironment. The ISR pathway plays a key role in these processes through its regulation of protein translation and maintenance of hematopoietic homeostasis. In AML, the ISR exhibits a dual role by balancing cell survival and apoptosis. ISR signaling exhibits a dual role in AML: under physiological conditions, it promotes LSC stemness and maintenance, contributing to leukemogenesis.[22] In contrast, therapeutic hyperactivation of ISR can trigger strong anti-leukemic responses.[23]

### ISR in AML: A Pathogenic Driver of Leukemogenesis and Disease Progression

#### ISR Regulates HSC Homeostasis and LSC Leukemogenesis

Under physiological conditions, HSCs maintain a delicate balance between self-renewal and differentiation through tightly regulated signaling pathways, thereby ensuring hematopoietic homeostasis over the long term. Research has shown that HSCs typically exhibit a basal ISR activation profile characterized by low eIF2 (due to accumulated phosphorylated eIF2α) and elevated ATF4 expression.[22] In response to external stressors, moderate ISR activation helps sustain HSC homeostasis and enhances stress resilience (Figure 2). For example, during amino acid deprivation, upregulation of the ATF4–eIF2α axis significantly promotes HSC survival and supports functional recovery. However, under severe stress conditions such as DNA damage, accumulation of reactive oxygen species (ROS), or exposure to ionizing radiation, excessive activation of the PERK–eIF2α-mediated ER stress pathway induces pro-apoptotic genes like CHOP, rendering HSCs more prone to apoptosis.[24,25] This mechanism serves to eliminate damaged HSCs, thereby preventing their malignant transformation and reducing the risk of leukemia. In addition, ISR-induced senescence of HSCs appears to hinder leukemic progression. Evidence from serial transplantation and fractionated low-dose ionizing radiation models suggests that activation of Ripk3 impairs mitochondrial ISR signaling via the OMA1–DELE1–HRI axis, suppressing the eIF2α–ATF4 pathway and promoting senescence in HSCs and pre-leukemic stem cells.[25] Likewise, ATF4 deficiency induces senescence-associated phenotypes in HSCs, including functional decline and myeloid-biased differentiation, further supporting the regulatory role of ISR in cellular aging.[26] Interestingly, during natural aging, the expression levels of ATF4 and phosphorylated eIF2α in HSCs remain unchanged, suggesting that ISR regulation may be context-dependent and selective across different physiological and pathological states.

In AML, the abnormal proliferation and self-renewal capacity of LSCs are key drivers of disease progression. Similar to HSCs, LSCs exhibit a pattern of low phosphorylated eIF2α and high ATF4 expression, which may be critical for maintaining their stem-like properties.[22] Moreover, elevated ISR activity in LSCs may reflect a more aggressive leukemic

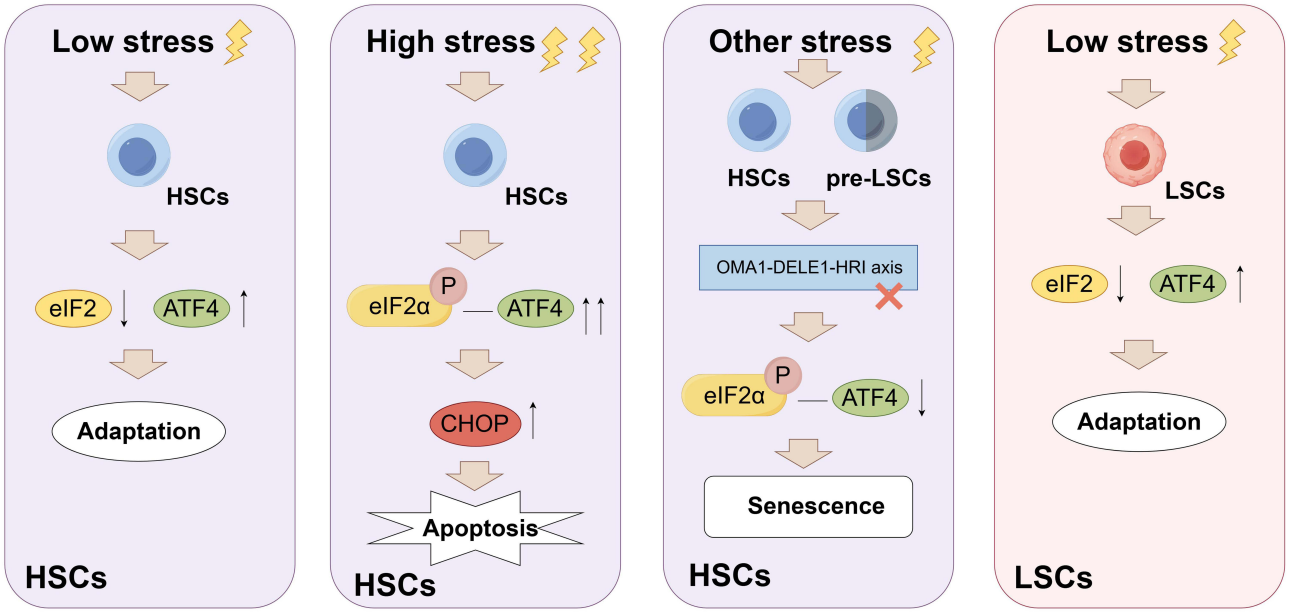


**Figure 2** Role of ISR in HSC homeostasis and LSC leukemogenesis. Under low stress conditions, such as amino-acid deprivation, accumulation of p-eIF2α suppresses eIF2 activity while enhancing ATF4 expression, promoting adaptive responses in both HSCs and LSCs. Under high stress conditions, including increased mitochondrial ROS and DNA damage, trigger strong ISR activation and induce apoptosis in damaged HSCs to preserve stem cell pool integrity. Other stressors, such as ionizing radiation and serial transplantation, impair the OMA1–DELE1–HRI axis in HSCs, reduce p-eIF2α/ATF4 signaling, and drive HSC senescence. Upward arrows denote activation or increased expression; downward arrows denote repression; double arrows denote strong or sustained ISR activation; × denotes pathway inhibition or inactivation.

phenotype and predict a poorer prognosis. Under stress conditions such as amino acid deprivation, the ISR enhances LSC survival by upregulating ATF4 expression and translation, thereby improving their adaptability to nutrient-deprived environments and promoting leukemogenesis.[22] Clinically, high ISR activity has been associated with adverse outcomes in AML.[27] These findings collectively suggest that modulating ISR may offer therapeutic potential by reducing LSC self-renewal and survival, while potentially mitigating HSC dysfunction in AML.

## Genetic and Transcriptional Dysregulation Rewire ISR Signaling to Drive AML Pathogenesis

Clonal mutations, epigenetic abnormalities, and splicing factor mutations are considered key mechanisms underlying preleukemic progression in AML[28] Recent studies indicate that genetic alterations affect the phenotypic divergence of HSCs and AML cells by modulating the eIF2α–ATF4 axis within the ISR pathway. Specifically, genetic and epigenetic dysregulations can drive leukemogenesis by modulating the eIF2α–ATF4 signaling cascade (Figure 3). RUNX1 mutations are prevalent in AML and are associated with poor prognosis, particularly in older patients.[29] Loss of RUNX1 methylation in HSCs suppresses p-eIF2α and ATF4 expression via the PERK pathway, thereby facilitating the transformation of HSCs into leukemic cells.[30] In $RUNX1^{R233K/R237K}$ double-mutant mice, mutations at two arginine-lysine residues impair methylation of RUNX1, resulting in downregulation of ATF4 mRNA. Furthermore, the Ripk3 signaling pathway is suppressed in AML cells with poor-prognosis mutations such as RUNX1-ETO or FLT3-ITD.[31] Activation of the RIPK3 pathway has been shown to simultaneously inhibit ISR activity and activate an MLKL-dependent pathway, thereby promoting HSC senescence and necroptosis, and ultimately preventing the transformation of pre-LSCs into LSCs.[25] Under stress conditions (eg, low-dose radiation or serial transplantation), TNF-α activates RIPK3 signaling. Activated RIPK3 enhances mitochondrial oxidative phosphorylation (OXPHOS) and mitochondrial reactive oxygen species production, thereby inhibiting the mitochondrial stress response pathway OMA1-DELE1-HRI and attenuating ISR activity. Reduced ISR relieves protein synthesis constraints, increasing HSC susceptibility to senescence and ultimately blocking the malignant transformation of damaged HSCs. Thus, genetic alterations that activate the ISR may promote the transformation of HSCs into preleukemic cells. Recent findings show that reduced Triad1 expression stabilizes Gcn1 and drives persistent activation of the GCN2–eIF2α–ATF4 ISR axis, promoting leukemogenesis in KMT2A-rearranged AML. Importantly, Gcn1 loss restores normal ISR signaling and delays disease progression,

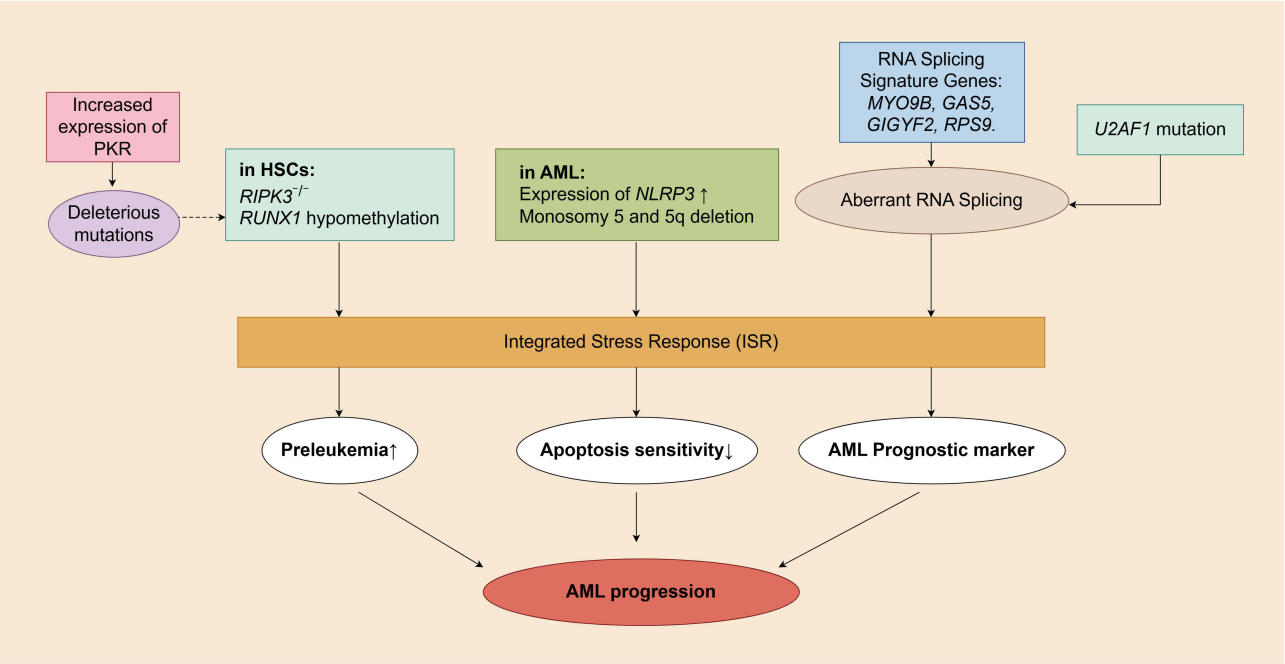


**Figure 3** Genetic and transcriptional dysregulation modulates ISR activity and contributes to AML progression. In HSCs, RIPK3 deficiency and RUNX1 hypomethylation promote pre-leukemic expansion through ISR-related mechanisms. In AML cells, NLRP3 overexpression and monosomy 5/5q deletion reduce apoptosis sensitivity, while U2AF1 mutation and RNA-splicing abnormalities further influence disease behavior via ISR modulation. All three ways influence AML progression through ISR modulation. Arrows denote causal or regulatory relationships; dashed lines represent indirect modulation; upward and downward arrows indicate relative increases or decreases in expression or activity.

highlighting Triad1–Gcn1 dysregulation as another genetic mechanism rewiring ISR activity in AML.[32] Interestingly, upregulation of PKR, a key ISR kinase, has been implicated in the accumulation of deleterious mutations in AML.[33] Elevated PKR expression in CD34+ AML cells correlates with poorer survival rates and shorter remission durations. Genetic knockout or functional loss of PKR reduces the frequency of spontaneous mutations in NUP98-HOXD13 mouse models, including mutations induced by aging, radiation, or potent oncogenes.

Additionally, genetic alterations reprogram mitochondrial stress-response pathways in AML cells, affecting their apoptotic susceptibility. High expression of NLRP3 is significantly associated with decreased overall survival in AML patients.[34] Notably, p-eIF2α is increased in NLRP3-deficient AML cells. Mice transplanted with NLRP3-knockout AML cells exhibit reduced leukemic burden. Inhibition of NLRP3 enhances PERK–eIF2α axis activity, thereby increasing AML cell sensitivity to apoptosis induced by pro-apoptotic BCL-2 family proteins. Monosomy 5 and deletion of chromosome 5q occur in approximately 5% of de novo AML cases and up to 40% of secondary AML cases. These chromosomal abnormalities are frequently accompanied by TP53 mutations and are associated with extremely poor prognosis. Among genes in the commonly deleted region of 5q-AML, DELE1—a mitochondrial stress response gene—is one of the most consistently downregulated.[35] Mitochondrial stress is normally conveyed to the cytoplasm via the OMA1-DELE1-HRI pathway, initiating apoptosis.[36] DELE1 deletion disrupts this mitochondrial stress signaling, impairing the HRI-mediated ISR pathway and resulting in failure to trigger apoptosis.

Splicing is an essential step in RNA processing that generates mature mRNA. Aberrant splicing includes both the mis-splicing of splicing factor genes and the abnormal splicing of their target transcripts. In AML, spliceosome dysfunction is relatively common, and dysregulated splicing can broadly promote tumorigenesis.[37] Abnormal splicing is also associated with drug resistance and poor prognosis. Anande G et al[27] reported that selective splicing of protein translation genes upregulates ISR and inflammation-related genes by analyzing differential gene expression profiles from the same patients in the European Leukemia Network database. Four genes with specific splicing events were identified as prognostic markers: *MYO9B, GAS5, GIGYF2*, and *RPS9*. The aberrant splicing characteristics of these genes help predict poor prognosis and enhance the risk stratification of AML patients. Similarly, *U2AF1* mutations are implicated in

the pathogenesis of multiple malignancies. These mutations activate ISR by disrupting the splicing of mRNA translation-related genes.[38] ISR activation enhances the adaptability of AML cells under stress, promoting resistance to chemotherapy. Treatment with ISRIB, an ISR inhibitor, has been shown to increase the chemosensitivity of *U2AF1*-mutant cells. Taken together, genetic and transcriptional dysregulation drives leukemogenesis and contributes to therapeutic resistance by modulating the ISR pathway, thereby suppressing mitochondrial apoptosis and reducing AML cell sensitivity to chemotherapeutic agents.

### ISR Activation Remodels Bone Marrow Niche in AML

The bone marrow niche is primarily categorized into the endosteal niche and the vascular niche.[39] Recent studies have demonstrated that AML cells can activate ISR pathway in bone marrow stromal cells through intercellular communication mechanisms such as extracellular vesicles (EVs), thereby remodeling both the endosteal and vascular niches to promote AML progression.

AML-induced osteogenic differentiation of MSCs has been shown to suppress normal hematopoiesis while conferring survival and proliferative advantages to leukemia cells.[40] Bone morphogenetic protein 2 (BMP2) is a potent inducer of osteogenic differentiation.[41] Doron B et al[42] found that BMP2 is transmitted to the bone marrow stroma via EVs, which activates ISR signaling in MSCs, as evidenced by upregulation of phosphorylated eIF2α and CHOP. This, in turn, enhances the osteogenic differentiation of MSCs and increases the expression of early osteogenic markers such as Runx2 and Osterix. Additionally, other studies have shown that activation of the PERK-eIF2α-ATF4 axis upregulates late-stage osteogenic genes such as osteocalcin and bone sialoprotein.[43] These findings collectively indicate that AML cells activate the ISR pathway in BM stromal cells, thereby remodeling the endosteal niche.

The vascular niche regulates AML cell survival through paracrine signaling and adhesion to endothelial cells. Notably, PKR, a central kinase in the ISR pathway, has been shown to suppress angiogenesis via downregulation of vascular endothelial growth factor signaling.[44] This suggests that the ISR pathway may influence angiogenesis-dependent mechanisms in AML by modulating endothelial cell function. In addition to PKR, the PERK arm of the ISR also plays a crucial role in remodeling the vascular niche and inducing endothelial cell apoptosis. Studies have revealed that exosomes secreted by T-cell acute lymphoblastic leukemia cells can be internalized by endothelial cells, activating the PERK-eIF2α-ATF4-JAG1 signaling axis.[45] SCF and CXCL12 are essential for the maintenance and regeneration of HSCs. Upregulation of JAG1 suppresses SCF and CXCL12 expression while promoting vascular endothelial growth factor α expression, thereby altering the vascular microenvironment. Further mechanistic studies have shown that knockout of PERK reverses JAG1 upregulation and significantly promotes apoptosis in leukemia cells, partially elucidating the role of the ISR pathway in remodeling the vascular niche in leukemia.

## ISR Pathway Enhances AML Sensitivity to Targeted and Chemotherapeutic Agents

Current treatments for AML include chemotherapy, targeted therapies, and stem cell transplantation. However, 30–40% of patients are refractory or relapse after initial therapy.[46] Recent evidence suggests that modulating the ISR can sensitize AML cells to venetoclax and daunorubicin, providing a potential strategy to overcome drug resistance.

### Reversal of Targeted Drug Resistance

Venetoclax, a BCL-2 inhibitor approved by the FDA for AML treatment, works by displacing pro-apoptotic BH3-only proteins from BCL-2, thus activating pro-apoptotic proteins BAX and BAK. As a novel targeted therapy, BCL-2 inhibitors have markedly improved early remission rates and overall survival in AML patients. However, approximately 34% of newly diagnosed AML patients exhibit primary resistance to venetoclax when combined with chemotherapy.[47] High expression of MCL-1 is frequently observed in venetoclax-resistant AML cells, leading to downregulation of the pro-apoptotic protein BAX.[48] Inhibiting or silencing MCL-1 restores venetoclax sensitivity in AML, suggesting MCL-1 as a viable therapeutic target.[49] However, a clinical trial investigating the MCL-1 inhibitor AMG 176 in combination with venetoclax for relapsed/refractory hematologic malignancies was terminated due to elevated serum cardiac troponin levels.[50] This may be attributed to the high expression of MCL-1 in the heart,[51] which likely contributes to the observed

cardiotoxicity in humans. Therefore, exploring alternative mechanisms to indirectly degrade MCL-1 in AML may offer a promising approach to mitigate venetoclax resistance.

Notably, ISR downstream signaling has demonstrated potential for selectively downregulating MCL-1 protein in AML, thereby overcoming resistance to venetoclax (Figure 4). The ISR pathway is initiated by four kinases: PERK, HRI, GCN2, and PKR. Once activated, these kinases phosphorylate eIF2α, leading to increased ATF4 expression and subsequent activation of downstream effectors, including CHOP, Cation Transport Regulator-like Protein 1 (CHAC1), DNA Damage-Inducible Transcript 4 (DDIT4, also named as REDD1), ATF3, and GRP78/BiP mRNA.[52–54] Among these, DDIT4 functions as an mTOR pathway inhibitor, which promotes AML cell apoptosis by suppressing mTORC1 activity.[55] In the cytoplasm, the BH3-only proteins PUMA, NOXA, BID, and BIM interact with BAX/BAK, disrupting mitochondrial membrane potential and facilitating cytochrome c release into the cytosol, thereby triggering apoptosis. MCL-1 inhibits apoptosis in AML cells by binding to BID and BIM. In ISR signaling, CHOP promotes the upregulation of NOXA, which antagonizes MCL-1, enabling BAX/BAK-dependent apoptosis and enhancing venetoclax sensitivity in AML cells.[56] Additionally, ISR activation also upregulates c-MYC, which induces PUMA expression through CHOP, further promoting apoptosis.[57]

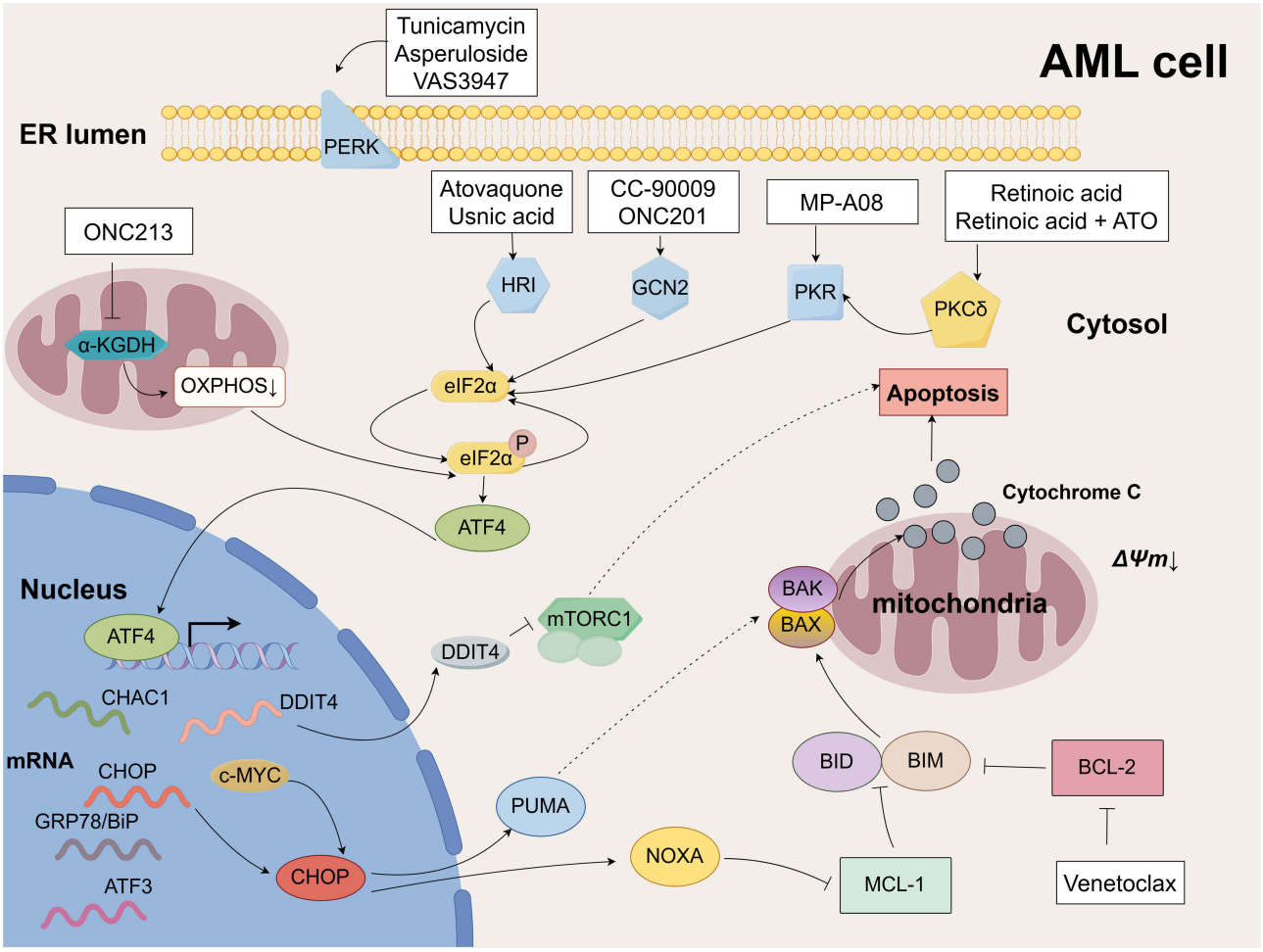


**Figure 4** ISR-activating agents and downstream apoptotic signaling in AML cells. Multiple compounds activate PERK, HRI, GCN2, or PKR, leading to p-eIF2α and ATF4 induction. ATF4 upregulates CHOP, CHAC1, DDIT4, ATF3, and GRP78/BiP, shaping metabolic and apoptotic responses. CHOP promotes NOXA expression, which inhibits MCL-1 and facilitates BAX/BAK-mediated mitochondrial apoptosis. PUMA, NOXA, Bid, and BIM activate BAX/BAK, triggering cytochrome c release and loss of mitochondrial membrane potential. MCL-1 restrains BID/BIM activity and contributes to Venetoclax resistance. Arrows denote activation or induction; blunt-end lines denote inhibition; $\Delta\Psi m\downarrow$ denotes reduced mitochondrial membrane potential.


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### Enhance the Efficacy of Chemotherapy

ABCB1 is a drug efflux pump implicated in resistance to daunorubicin. Williams MS et al[58] found that activation of the ISR in primary AML cells leads to ATF4 binding to the E3 enhancer region of the ATP Binding Cassette Subfamily B Member 1 (ABCB1) gene, thereby activating the enhancer and significantly upregulating ABCB1 expression, which promotes resistance to daunorubicin. Notably, ISR-mediated ABCB1 expression is dynamic: it increases rapidly under stress conditions like daunorubicin exposure and decreases gradually once the stress subsides. This flexible regulatory mechanism enables leukemic cells to modulate ABCB1 expression in response to environmental stimuli, facilitating adaptation to chemotherapy-induced stress and sustaining drug resistance. These findings suggest that inhibition of key components in the ISR pathway may enhance the chemosensitivity of AML cells to daunorubicin.

However, excessive activation of the ISR pathway has also been shown to increase AML cell sensitivity to chemotherapeutic agents such as daunorubicin. DNAJC10 is highly expressed in various AML cell types and is associated with poor overall survival in AML patients. Li M et al[59] reported that loss of DNAJC10 activates the PERK-eIF2α-CHOP axis, thereby enhancing AML cell sensitivity to daunorubicin and cytarabine. These findings suggest that DNAJC10 may regulate sensitivity to these agents via modulation of the ISR pathway. Additionally, transient receptor potential melastatin 2 is highly expressed in AML and provides protective effects to leukemic cells. In transient receptor potential melastatin 2-knockout AML cells, mitochondrial dysfunction and elevated levels of reactive oxygen species (ROS) were observed, along with significant upregulation of transcription factors including ATF4, HIF-1/2α, Nrf2, and CREB. These changes collectively heightened the sensitivity of AML cells to doxorubicin.[60]

## Targeting the Integrated Stress Response as a Therapeutic Strategy for AML

The aforementioned findings underscore the critical role of the ISR pathway in the pathogenesis of AML and in improving treatment outcomes, suggesting that targeting the ISR represents a promising therapeutic strategy. Multiple studies have demonstrated that both monotherapy (Figure 5) and combination therapies can modulate ISR activity in AML cells. These treatments include classic anti-AML drugs, repurposed agents, investigational compounds, and drugs currently undergoing clinical trials (Tables 1 and 2).

## Promising Drugs for Targeting the ISR Pathway in AML

### Hypomethylating Agents

HMAs exert their antileukemic effects by inhibiting DNA methyltransferase activity, thereby reversing aberrant DNA methylation and reactivating silenced genes through epigenetic mechanisms.[74] Clinically, HMAs such as azacitidine and decitabine have shown enhanced therapeutic efficacy when combined with the BCL-2 inhibitor venetoclax, significantly deepening remission and prolonging survival in patients. Despite the clinical success of this combination, the molecular mechanisms underlying its synergistic effects remain incompletely understood. Jin S et al[61] demonstrated that the combination of 5-azacitidine and venetoclax exerted potent synergistic cytotoxic effects in AML cell lines and confirmed its antitumor efficacy in animal models. Mechanistic studies revealed that 5-azacitidine monotherapy specifically activates the ISR pathway, significantly upregulating proapoptotic proteins NOXA and PUMA via the ATF4/CHOP axis. NOXA, a key negative regulator of MCL-1, binds to MCL-1 and promotes its ubiquitination and degradation, thereby enhancing apoptosis sensitivity. Further experiments showed that knockout of *NOXA* substantially diminished the proapoptotic effect of the combination treatment, whereas *PUMA* deletion did not confer a comparable degree of resistance.

Homoharringtonine (HHT), an alkaloid derived from the plant *Cephalotaxus*, is often used in combination with chemotherapeutic agents such as cytarabine.[75] HHT demonstrates promising efficacy in elderly AML, pediatric AML, FLT3-ITD AML, and refractory/relapsed AML.[76–79] Studies have shown that treatment with azacitidine plus HHT induces p-eIF2α and upregulation of ATF4, ultimately increasing expression of ISR-mediated apoptotic effectors DDIT3 and PUMA.[57] Moreover, inhibition of ISR signaling or knockdown of *DDIT3* or *PUMA* significantly attenuated the

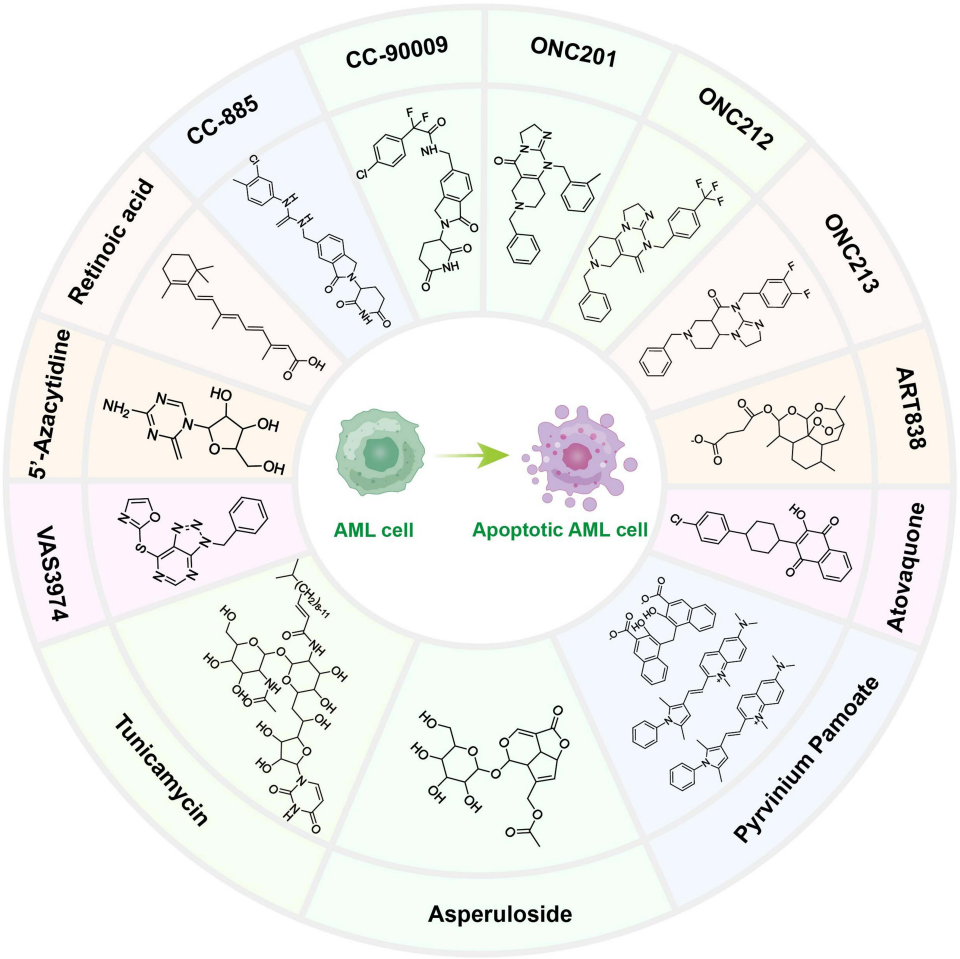


**Figure 5** Chemical Structures of Compounds Targeting the ISR Pathway to Induce Apoptosis in AML. These compounds activate the ISR pathway through both monotherapy and/or combination therapy in AML cells.

proapoptotic effect of azacitidine + HHT in AML cells. These findings highlight the critical role of ISR signaling in the antileukemic activity of azacitidine monotherapy and its combinations with venetoclax or HHT.

## ATRA

All-trans retinoic acid (ATRA) is a standard therapeutic agent for acute promyelocytic leukemia (APL), promoting the differentiation of leukemic cells into mature granulocytes. It is typically administered in combination with arsenic trioxide (ATO), a regimen that has markedly improved the prognosis of APL patients.[80] Research has shown that ATRA can drive granulocytic differentiation of myeloid leukemia cells via the PKCδ/PKR/eIF2α signaling pathway.[62] Furthermore, ATRA combined with ATO activates PKCδ, which subsequently activates PKR—rather than GCN2 or PERK—leading to p-eIF2α.[81] Additional studies have demonstrated that ATRA significantly enhances the sensitivity of APL cells to ER stress inducer tunicamycin, primarily through activation of the PERK pathway.[82] PERK activation by tunicamycin results in p-eIF2α, which suppresses global protein translation while promoting ATF4 translation and the subsequent upregulation of proapoptotic genes such as CHOP. Concurrently, low-dose tunicamycin-induced ER stress significantly amplifies ATO toxicity. In both ATRA-sensitive and ATRA-resistant APL cell lines, the combination of ATO and tunicamycin yields synergistic cytotoxicity, closely linked to elevated oxidative stress levels. These findings underscore the pivotal role of the ISR in the therapeutic response of APL to ATRA and ATO. By leveraging different cellular stressors to activate PERK, the therapeutic effects of this regimen are enhanced. This synergistic interaction not only boosts efficacy but also reduces toxicity, offering a safer and more effective treatment strategy for APL.


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**Table 1** Monotherapy Targeting the ISR Pathway in AML

| Drug | Drug Group | Monotherapy | ISR Target | Action on ISR | Phenotype | References |
|---|---|---|---|---|---|---|
| 5-Azacytidine | Hypomethylating agents | 5-Azacytidine | NA | ↑p-eIF2α<br>↑ATF4 translation<br>↑CHOP translation | NOXA-mediated apoptosis<br>↑PUMA transcription and translation | [61] |
| Retinoic acid | Differentiation inducer | Retinoic acid | PKR | ↑p-eIF2α | Promote myeloid leukemia cell granulocytic differentiation | [62] |
| Atovaquone | Antiparasitic Agents | Atovaquone | HRI and PERK | ↑p-eIF2α<br>↑ATF4 translation | Apoptosis in AML cells and AML patient-derived sample cells<br>↓OXPHOS | [51] |
| Pyrvinium Pamoate | Antiparasitic Agents | Pyrvinium Pamoate | PERK and GCN2-independent | ↑p-eIF2α<br>↑ATF4 translation | Apoptosis in Molm13-XR (cabotinib resistance) cells | [63] |
| ART838 | Antiparasitic Agents | ART838 | NA | ↑CHOP protein expression | Apoptosis in AML cells<br>↓MCL-1 protein expression | [53] |
| CC-885 | GSPT1 degradation agent | CC-885 | NA | ↑p-eIF2α<br>↑ATF4 transcription and translation | TP53-independent apoptosis in AML cells | [64] |
| CC-90009 | GSPT1 degradation agent | CC-90009 | GCN2 | ↑p-eIF2α<br>↑ATF3 and ATF4 mRNA | Apoptosis in AML cells<br>mTOR pathway activation reduced anti-leukemia activity<br>TP53-independent apoptosis in AML cells | [64–66] |
| AB138 | GSPT1 degradation agent | AB138 | NA | ↑p-eIF2α<br>↑ATF4 translation<br>↑CHOP translation | Apoptosis in AML cells;<br>↓MCL-1 protein expression;<br>↓c-Myc protein expression | [67] |
| ONC201 | Imipridones | ONC201 | GCN2 | ↑p-eIF2α<br>↑ATF4, CHOP translation | Apoptosis in AML cells<br>↓MCL-1 protein expression | [65,66] |
| ONC212 | Imipridones | ONC212 | NA | ↑p-eIF2α<br>↑ATF4 translation<br>↑CHOP transcription | Apoptosis in AML cells<br>↓MCL-1 protein expression<br>↓NOXA-mediated MCL-1 protein expression | [68,69] |
| ONC213 | Imipridones | ONC213 | NA | ↑p-eIF2α<br>↑ATF4 translation | Apoptosis in AML cells<br>↓α-KGDH activity<br>↓MCL-1 protein expression | [70,71] |
| Tunicamycin | ER stress inducer | Tunicamycin | PERK | ↑CHOP mRNA | Apoptosis in AML cells | [72] |
| Asperuloside | TCM active compound | Asperuloside | PERK | ↑p-eIF2α<br>↑CHOP translation | GRP78-mediated apoptosis in AML cells | [54] |
| VAS3947 | NOX inhibitors | VAS3947 | PERK | ↑p-eIF2α | Apoptosis in AML cells | [73] |

**Notes**: ↑ denotes increased expression or activation; ↓ denotes decreased expression or suppression.
**Abbreviations**: NA, Not applicable; p-eIF2α, eIF2α phosphorylation; TCM, Traditional Chinese Medicine; NOX inhibitors, NADPH oxidase inhibitors.

**Table 2** ISR-Targeting Agents That Have Entered Clinical Trials in AML

| Drug | Phase | Identifier | Conditions | Sponsor | Status |
|---|---|---|---|---|---|
| Atovaquone | Early Phase 1 | NCT03568994 | AML | Baylor College of Medicine | Active, not recruiting |
| CC-90009 | Phase 1 | NCT04297124 | Healthy volunteer | Celgene | Completed |
| | Phase 1 | NCT02848001 | AML | Celgene | Terminated |
| | Phase 1, 2 | NCT04336982 | AML | Celgene | Terminated |
| ONC201 | Phase 1 | NCT03932643 | AML | University of Nebraska | Active, not recruiting |
| | Phase 1, 2 | NCT02392572 | R/R AML | M.D. Anderson Cancer Center | Recruiting |

## Antiparasitic Agents

Atovaquone, an antimalarial drug approved by the FDA in 1999 for the treatment of pneumocystis pneumonia, has recently demonstrated notable antileukemic potential. It induces apoptosis in the majority of AML cell lines and significantly reduces disease burden in AML xenograft models, thereby prolonging overall survival.[52] Mechanistically, Atovaquone upregulates ATF4 and its downstream targets, including proapoptotic genes such as CHOP and CHAC1, while concurrently inhibiting the mTOR signaling pathway. This dual action promotes apoptotic cell death in AML cells. Furthermore, Atovaquone disrupts OXPHOS, decreasing oxygen consumption and selectively targeting chemotherapy-resistant AML cells that rely on OXPHOS for survival. Clinical trials investigating Atovaquone in AML are currently ongoing. An active trial is evaluating its efficacy in combination with standard chemotherapy in pediatric AML.[83] Preliminary data suggest that Atovaquone is well-tolerated across pediatric age groups, with no significant adverse effects observed. Additionally, a retrospective study reported a potential association between prolonged Atovaquone use for Pneumocystis prophylaxis in AML patients undergoing hematopoietic stem cell transplantation and improved relapse-free survival.[84] Collectively, these findings underscore Atovaquone's therapeutic potential, particularly in pediatric AML.

Pyrvinium pamoate, a classical anthelmintic drug, has recently emerged as a promising anticancer agent. Fu Y-H et al[63] demonstrated that Pyrvinium pamoate significantly inhibits the proliferation of FLT3-ITD-mutant Molm13 cells, with a nanomolar IC50 (50.15 ± 0.43 nM). Transcriptomic analyses revealed that Pyrvinium pamoate activates the ISR, upregulates the eIF2α-ATF4 signaling axis, and concurrently suppresses mTORC1 activity, leading to cell cycle arrest and apoptosis. Moreover, Pyrvinium pamoate localizes to mitochondria and inhibits mitochondrial respiratory complex I, resulting in reduced basal respiration and ATP production, as well as elevated intracellular ROS levels and mitochondrial dysfunction. These effects were observed not only in Molm13 cells but also in cabozantinib-resistant Molm13-XR cells. In vivo studies further confirmed that Pyrvinium pamoate significantly suppresses the growth of Molm13 and Molm13-XR xenografts and prolongs survival. These findings suggest that Pyrvinium pamoate exerts its antileukemic activity by modulating mitochondrial function and activating the ISR, providing a potential therapeutic strategy for FLT3-ITD-mutant AML.

ART838, a derivative of artemisinin, has been shown to exhibit synergistic antitumor activity with sorafenib in the MOLM14 AML cell line.[85] Moses BS et al[53] demonstrated that ART838 induces apoptosis in AML cell lines with poor prognostic profiles, such as MOLM14 and MV4;11. Mechanistic studies revealed that ART838 activates the ISR pathway, significantly increasing the expression of CHOP at both the mRNA and protein levels, which in turn down-regulates MCL-1 expression. Furthermore, ART838 exhibits synergistic effects with Venetoclax in vitro. In vivo, the combination of ART838, Venetoclax, and sorafenib markedly reduces leukemia burden in MOLM14 and MV4;11 xenograft models and significantly extends survival. Importantly, no significant toxicity was observed during treatment, indicating a favorable safety profile.

## GSPT1 Degradation Agent

GSPT1 (GTPase-activating protein-shuttling factor 1) degraders are a class of small molecules that selectively target GSPT1 protein for degradation and have emerged as potential cancer therapeutics.[86] In recent years, therapeutic strategies targeting proteostasis dysregulation have gained increasing attention, and GSPT1 degraders have been shown to eliminate the translation-termination factor, rapidly activate the ISR, and induce apoptosis in AML cells.[87]

Several GSPT1 degraders have been identified to activate the ISR pathway. CC-885, first reported in 2016, demonstrated potent antitumor activity in patient-derived AML cells.[88] It degrades GSPT1, thereby activating the ISR and impairing translation termination in AML cells. This process upregulates DDIT4 expression and induces TP53-independent cell death.[64] However, due to its off-target effects, development of CC-885 was discontinued.

CC-90009, a next-generation cereblon-based GSPT1 degrader, exhibits improved target specificity compared to CC-885.[89] It induces potent proapoptotic effects in both AML cell lines and primary AML patient samples.[90–92] Mechanistically, CC-90009 activates the ISR via the GCN1/GCN2/eIF2α/ATF4/DDIT4 signaling axis. Genetic knockout experiments confirmed that GCN2 and DDIT4 are essential mediators of its antileukemic activity. CC-90009 has also demonstrated synergistic activity with multiple targeted agents in AML. Preclinical data show enhanced efficacy when combined with FLT3 inhibitors midostaurin, BCL-2 inhibitor venetoclax, or IDH2 inhibitors.[93] Colony formation assays using primary AML samples revealed that combination regimens significantly suppress leukemic growth compared to monotherapies. These findings were corroborated in vivo using FLT3-ITD patient-derived xenograft (PDX) models, where the combination of quizartinib and CC-90009 significantly prolonged survival. Furthermore, triple therapy with Venetoclax, azacitidine, and CC-90009 achieved superior survival outcomes relative to single or dual-agent regimens. Currently, CC-90009 is under clinical investigation for AML. Phase I trials have confirmed its capacity to induce robust GSPT1 degradation with an acceptable safety profile.[94] Additional ongoing trials are evaluating its efficacy in combination regimens and pharmacokinetics in healthy volunteers.[95,96] Collectively, these findings highlight CC-90009 as a promising ISR-activating agent with broad therapeutic potential and clinically actionable synergy in AML treatment.

Recent studies show that the novel GSPT1 degrader AB138 efficiently eliminates GSPT1 at nanomolar concentrations, accompanied by eIF2α phosphorylation and ATF3/CHOP upregulation, leading to rapid depletion of MCL1 and c-Myc and caspase-3–dependent apoptosis. Consequently, AB138 exhibits potent anti-leukemic activity both in vitro and in vivo, further supporting the therapeutic potential of GSPT1-targeted degraders as a next-generation proteostasis-modulating strategy.[67]

### Imipridones

ONC201 is a first-in-class imipridone compound that exerts antitumor effects in AML by disrupting mitochondrial function. Ishizawa J et al[65] demonstrated that ONC201 uniquely induces an atypical integrated stress response (ISR) alongside a p53-independent intrinsic apoptosis pathway. Mechanistically, ONC201 induces p-eIF2α in AML cells; intriguingly, ATF4 is upregulated via an eIF2α-independent mechanism. This cascade leads to increased expression of DDIT4, a key ATF4 downstream target, which suppresses mTORC1 signaling and triggers apoptotic cell death. Notably, ONC201 exhibits synergistic antileukemic activity when combined with the BCL-2 inhibitor venetoclax. Similar synergistic effects are observed in combination with conventional chemotherapeutic agents such as cytarabine and azacitidine.[66] ONC201 is currently undergoing early-phase clinical evaluation in AML patients, showing encouraging therapeutic potential.[97,98]

ONC212, a second-generation imipridone, exhibits enhanced antitumor efficacy compared to ONC201. ONC212 induces apoptosis in AML cells by activating the ISR pathway and downregulating the anti-apoptotic protein MCL-1.[68,69] Overexpression of MCL-1 has been implicated in resistance to BCL-2 inhibitors in AML. In NSG PDX models, the combination of ONC212 and venetoclax displayed pronounced synergistic antileukemic activity. ONC212 also demonstrates strong antiproliferative effects against human leukemia cells while sparing normal hematopoietic cells, suggesting favorable selectivity. Although not yet in clinical trials, current preclinical evidence positions ONC212 as a highly promising candidate for AML therapy.

ONC213, another imipridone analog, has recently been shown by Su Y et al[70] to induce apoptosis in AML cells in vitro, reduce leukemic burden, and prolong survival in AML xenograft mouse models. Mechanistic investigations reveal that ONC213 inhibits α-ketoglutarate dehydrogenase (α-KGDH), thereby suppressing oxidative phosphorylation (OXPHOS) and activating the ISR. During this process, MCL-1 protein levels are translationally downregulated, contributing to apoptosis.

### Other Drugs in Preclinical Research

Several small-molecule compounds capable of activating the ISR have demonstrated antileukemic activity in preclinical models, although they have not yet entered clinical trials. Tunicamycin, a glucosamine-containing antibiotic, inhibits N-glycosylation and induces ER stress, exerting both antimicrobial and antileukemic effects. Tsitsipatis D et al[72] reported that low-dose tunicamycin disrupts glycoprotein maturation of FLT3-ITD, producing potent antiproliferative and pro-apoptotic effects in FLT3-ITD-mutated AML cell lines. Mechanistically, tunicamycin induces apoptosis via dual pathways: it traps FLT3-ITD in a hypoglycosylated form, attenuating AKT/ERK signaling, and activates the PERK/CHOP axis. Pharmacological inhibition of PERK decreases CHOP expression and partially rescues cell viability, confirming the functional contribution of the PERK/CHOP pathway. Furthermore, tunicamycin synergizes with FLT3-ITD kinase inhibitors, showing selective cytotoxicity against FLT3-ITD-positive AML cell lines and primary blasts.

Asperuloside, an iridoid glycoside derived from the traditional herbal remedy dandelion, has been shown by Chao Rong et al[54] to induce intrinsic apoptosis in AML cell lines and primary cells. This is associated with the upregulation of GRP78 and ISR markers including PERK, phosphorylated eIF2α, and CHOP. Separately, the NADPH oxidase inhibitor VAS3947 induces apoptosis by activating PERK and the ER stress sensor IRE1α.[73] Collectively, these small molecules exhibit promising antileukemic effects via modulation of the ISR pathway, though further studies are needed to evaluate their clinical applicability.

## Targeting ISR to Overcome Venetoclax Resistance in AML

Several ISR-activating agents have demonstrated the ability to reverse venetoclax resistance in AML when used in combination therapy. These agents include gilteritinib, usnic acid, and sphingosine kinase 1 (SPHK1) inhibitors such as MP-A08 and ONC213 (Table 3).

### Gilteritinib

Gilteritinib, a second-generation FLT3 inhibitor, is primarily used to treat patients with relapsed or refractory AML, particularly in patients with FLT3 mutations.[100] A phase 1b trial reported that venetoclax plus gilteritinib elicited

**Table 3** Summary of Combination Therapies Targeting the ISR Pathway to Overcome Resistance in AML Targeted Treatments

| Drug | AML Type | ISR Target | Action on ISR | Phenotype | References |
|---|---|---|---|---|---|
| Gilteritinib + venetoclax | Venetoclax-insensitive SKNO-1 cell line | NA | ISRIB significantly restores; SKNO-1 viability | Apoptosis in SKNO-1 cell line; ↓MCL-1, BCL-XL translation | [9] |
| Tedizolid + venetoclax; Tedizolid + venetoclax + azacitidine | Venetoclax resistant AML cell | NA | ↑p-eIF2α; ↑ATF4 translation; ↑CHOP translation | Apoptosis in AML cells; ↓mitochondrial translation | [23] |
| MP-A08 + Venetoclax | Venetoclax resistant AML cell; | PKR | ↑ATF4 translation | Apoptosis in AML cells; ↑NOXA translation ↓MCL-1 translation; | [99] |
| ONC213 + venetoclax | Venetoclax resistant AML cell; Venetoclax + Azacitidine resistant AML cell | NA | ↑p-eIF2α; ↑ATF4 translation | Apoptosis in AML cells; ↓MCL-1 translation | [71] |
| Usnic acid + venetoclax | Venetoclax resistant AML cell; | HRI | ↑ATF4 translation; ↑CHOP translation | Apoptosis in AML cells; ↑NOXA translation ↓MCL-1 translation; Reduced leukemia burden; ↓human CD45+ leukemia cells in the bone marrow | [7] |

**Notes**: ↑ denotes increased expression or activation; ↓ denotes decreased expression or suppression.
**Abbreviations**: NA, Not applicable; p-eIF2α, eIF2α phosphorylation; AML, acute myeloid leukemia; ISR, integrated stress response; MCL-1, myeloid cell leukemia-1; BCL-XL, B-cell lymphoma-extra large.


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significant clinical responses in relapsed or refractory AML patients.[101] Our clinical case reports indicated that a triple combination of gilteritinib, venetoclax, and azacitidine markedly reduced the proportion of peripheral blood blasts from 84% to 3.0% in relapsed/refractory AML patients who were FLT3 wild-type and AML1-ETO positive.[9] The synergistic effects and mechanisms of this combination were further examined in SKNO-1 cells insensitive to venetoclax. Mechanistically, the gilteritinib–venetoclax combination showed synergistic cytotoxicity in SKNO-1 cells, accompanied by downregulation of MCL-1 and BCL-XL; this effect was reversed by ISRIB, indicating ISR involvement.

Independent studies have confirmed similar results. High-throughput drug screening identified gilteritinib as the most synergistic partner of venetoclax in FLT3–wild-type AML, enhancing apoptosis and overcoming venetoclax–azacitidine resistance through dual FLT3/AXL inhibition and MCL-1 degradation.[8] Consistent preclinical and early clinical data also showed reduced leukemic burden in relapsed/refractory AML and MDS patients with FLT3–wild-type disease treated with the combination of venetoclax and gilteritinib.[102] Together, these findings support that ISR activation contributes to the synergy between gilteritinib and BCL-2 inhibition by promoting MCL-1 downregulation and enhancing therapeutic efficacy in venetoclax-resistant AML.

### Tedizolid

Tedizolid is a novel oxazolidinone antibiotic known to pharmacologically inhibit mitochondrial protein synthesis. According to a study by Sharon et al,[23] the combination of tedizolid and venetoclax effectively overcomes venetoclax resistance in AML, both in vitro and in vivo. Mechanistic investigations revealed that this combination robustly activates the ISR pathway, suppresses glycolytic capacity, impairs mitochondrial respiration, and ultimately induces an energy crisis leading to apoptosis. Notably, ISRIB-mediated inhibition of ISR significantly mitigated the pro-apoptotic effects of the combination therapy in AML cells. Although MCL-1 overexpression is a recognized contributor to venetoclax resistance, tedizolid treatment did not significantly alter the expression of BIM, MCL-1, or other BCL-2 family members. Furthermore, the sensitivity to the tedizolid–venetoclax combination persisted even after CRISPR-Cas9-mediated knockout of BIM, suggesting that ISR activation may occur independently of the MCL-1/BIM axis. A systems biology analysis integrating mathematical modeling and experimental data further supported this conclusion, showing that the combination enhances apoptotic signaling through alternative mechanisms despite stable MCL-1 levels.[103] Tedizolid has been FDA-approved for treating acute bacterial skin and skin structure infections caused by susceptible Gram-positive bacteria in adults. Clinical reports have demonstrated its efficacy in managing infections in relapsed AML patients with meningitis and bacteremia caused by extensively drug-resistant *Enterococcus faecalis*. Another report highlighted tedizolid as a safer option for treating toxic shock syndrome in patients with chronic myeloid leukemia.[104] Collectively, these findings support the use of tedizolid for infection control in leukemia patients without inducing myelosuppression.

### Other Novel Drugs

SPHK1 promotes ceramide accumulation. Lewis AC et al[99] found that the SPHK1 inhibitor MP-A08 induces ceramide accumulation in AML cells, triggering p-eIF2α via the PKR pathway, which subsequently activates ATF4. This activation leads to increased NOXA protein expression, degradation of the anti-apoptotic protein MCL-1, and induction of apoptosis in AML cells. The combination of the SPHK1 inhibitor MP-A08 and venetoclax effectively induced apoptosis in primary AML cells resistant to venetoclax.

As discussed earlier, ONC213 induces mitochondrial stress by inhibiting α-KGDH and downregulates MCL-1, thereby promoting apoptosis in AML cells. Since MCL-1 upregulation is a well-known mechanism of venetoclax resistance, researchers evaluated ONC213 in combination with venetoclax. Carter JL et al[71] demonstrated that ONC213 restores venetoclax sensitivity in resistant AML cells by activating the ISR pathway. In both in vitro and in vivo models, the combination of ONC213 and venetoclax synergistically eliminated AML cells resistant to venetoclax monotherapy or venetoclax plus azacitidine, and significantly reduced LSCs in PDX models. ISRIB treatment partially reversed the ONC213+venetoclax-induced downregulation of MCL-1.

Usnic acid, a dibenzofuran compound extracted from the lichen *Usnea diffracta Vain*, was shown to resensitize venetoclax-resistant AML cells.[7] In xenograft models using MOLM-13R cells, the combination of usnic acid and

venetoclax significantly reduced leukemia burden and decreased the percentage of human $CD45^+$ leukemic cells in the bone marrow. Mechanistically, low-toxic doses of usnic acid activated HRI kinase, resulting in the upregulation of ISR-related factors (ATF4, CHOP, NOXA), MCL-1 degradation, and apoptosis induction. Inhibition of the ISR pathway by ISRIB reversed these effects, including the increased expression of ISR-related genes and MCL-1 downregulation. Consistent with these findings, pharmacologic activation of the ISR by MP-A08, ONC213, or usnic acid activates the eIF2α–ATF4 pathway, upregulates NOXA, promotes MCL-1 degradation, and restores venetoclax sensitivity in resistant AML models, supporting this mechanism as a potential therapeutic route.

### Potential Biomarkers of ISR Therapies

ISR-targeting strategies have shown the ability to induce apoptosis or restore venetoclax sensitivity in multiple experimental models.These findings support their potential for further clinical development. Current evidence shows that hyperactivation of ISR leads to NOXA upregulation and MCL-1 reduction. High MCL-1 expression has been implicated in reduced sensitivity to venetoclax. This suggests that MCL-1 levels may serve as a useful marker of whether ISR activators can enhance venetoclax sensitivity or reverse resistance. However, upstream biomarkers that reflect ISR activation remain limited. It will also be important to evaluate ATF4 expression and p-eIF2α in AML patients treated with different ISR-activating agents. This would help delineate ISR activation status and guide patient stratification and response assessment.

### Limitations and Safety Concerns of ISR Therapies

Despite the promising therapeutic potential of ISR modulation in AML, important safety and mechanistic issues must be considered. Preclinical studies show that excessive or sustained ISR activation can trigger organ-specific toxicities, such as cardiomyopathy mediated by eIF2α-GCN2–ATF4 signaling in cardiac cells.[105] In the hematopoietic system, ISR activity is essential for maintaining stem cell survival during mild metabolic stress.[22] But severe or prolonged stress signaling has been shown to drive apoptosis of hematopoietic stem and progenitor cells, suggesting that excessive ISR activation may disrupt normal hematopoietic homeostasis. These observations highlight the need for careful evaluation of dose, duration, and tissue-specific responses when developing ISR-activating therapies for AML.

## Conclusions

For decades, a major challenge in AML treatment remains relapse. Recent studies suggest that a comprehensive treatment strategy integrating various therapeutic modalities targeting distinct adaptive pathways may offer more durable responses.[106] ISR is a key signaling pathway that enables cells to adapt to both external and internal stressors by globally reducing protein synthesis. In contrast, hyperactivation of ISR can induce apoptosis or restore venetoclax sensitivity. The findings reviewed in this study suggest that modulating ISR to sensitize AML cells to cellular stress may improve the effectiveness of chemotherapy and targeted therapies. ISR modulation may also weaken the protective role of the bone marrow microenvironment and LSCs in relapse and treatment resistance, thus providing a novel therapeutic direction for AML.

To facilitate clinical translation, several priorities should be emphasized: (i) prospective evaluation of ISR-modulating agents, alone or in combination with venetoclax-based regimens, particularly in relapse or refractory settings; (ii) incorporation of biomarker-guided approaches, including ATF4 signatures, p-eIF2α status, and NOXA/MCL-1 dynamics, to refine patient selection; and (iii) monitoring of safety signals associated with excessive or sustained ISR activation. (iv) integrating network pharmacology and AI-assisted screening to uncover ISR-targeting natural compounds with potential relevance to AML therapy.[107] Continued investigation along these directions will help define where ISR-targeting strategies may complement existing therapies and ultimately contribute to improved long-term management and survival in AML.

## Abbreviations

AML, Acute Myeloid Leukemia; HSCs, Hematopoietic Stem Cells; LSCs, Leukemia Stem Cells; ISR, Integrated Stress Response; eIF2, Eukaryotic Initiation Factor 2; eIF2α, Eukaryotic Initiation Factor 2 Alpha Subunit; p-eIF2α,

Phosphorylation of eIF2α; GCN2, General Control Nonderepressible 2; PKR, Protein Kinase R; HRI, Heme-Regulated Inhibitor; PERK, PKR-like Endoplasmic Reticulum Kinase; ATF4, Activating Transcription Factor 4; CHOP, C/EBP Homologous Protein (DDIT3); GADD34, Growth Arrest and DNA Damage-Inducible Protein 34 (PPP1R15A); ISRIB, Integrated Stress Response Inhibitor; ROS, Reactive Oxygen Species; OXPHOS, Oxidative Phosphorylation; ER, Endoplasmic Reticulum; EVs, Extracellular Vesicles; MCL-1, Myeloid Cell Leukemia-1; BAX, BCL-2-Associated X Protein; BAK, BCL-2 Antagonist/Killer; BH3, BCL-2 Homology Domain 3; ATRA, All-Trans Retinoic Acid; ATO, Arsenic Trioxide; HMA, Hypomethylating Agent; HHT, Homoharringtonine; FLT3, FMS-Like Tyrosine Kinase 3; ITD, Internal Tandem Duplication; PDX, Patient-Derived Xenograft; GSPT1, GTPase-Activating Protein-Shuttling Factor 1; α-KGDH, Alpha-Ketoglutarate Dehydrogenase; SPHK1, Sphingosine Kinase 1.

## Consent for Publication

This paper does not contain any individual person's data in any form. Therefore, obtaining written informed consent for publication was not applicable.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest.

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