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Tumor Discovery

ORIGINAL RESEARCH ARTICLE

Overcoming cisplatin resistance in ovarian cancer by targeting IFIT1-mediated inflammation responses

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Abstract

Ovarian cancer is a highly lethal malignancy, with treatment efficacy frequently compromised by the development of cisplatin resistance. This study investigates the molecular mechanisms driving cisplatin resistance, focusing on interferon-induced protein with tetratricopeptide repeats 1 (*IFIT1*), a key interferon-stimulated gene. Through comprehensive transcriptome profiling, we systematically compared gene expression patterns between cisplatin-sensitive and cisplatin-resistant ovarian cancer cells, identifying a consistent upregulation of *IFIT1* in resistant cells. Functional assays provided evidence that *IFIT1* plays a central role in mediating cisplatin resistance. Mechanistically, *IFIT1* was found to be associated with activation of inflammatory signaling pathways, suggesting its involvement in resistance-related immune regulation. Clinically, elevated *IFIT1* expression significantly correlated with an unfavorable prognosis in ovarian cancer patients. Moreover, we demonstrated that hypoxia-inducible factor-1 alpha transcriptionally regulates *IFIT1*, linking its expression to hypoxia response. Overall, these findings identify IFIT1 as a key driver of cisplatin resistance in ovarian cancer, shedding light on its clinical significance and the regulatory networks underpinning therapy resistance. *IFIT1* holds promise both as a prognostic indicator and as a target for therapeutic intervention. However, its clinical translation will depend on rigorous validation and in-depth exploration.

Keywords: Cisplatin resistance; Ovarian cancer; Interferon-induced protein with tetratricopeptide repeats 1; Gene expression; Inflammatory pathways; Hypoxia

1. Introduction

Ovarian cancer presents an enduring challenge within the realm of oncology, characterized by late-stage diagnosis and a limited array of therapeutic options that collectively contribute to alarmingly high mortality rates.[1] Among available treatments, cisplatin remains central to ovarian cancer therapy.[2] However, acquired resistance markedly increases the challenge of managing this aggressive malignancy.[3] Unraveling the intricate molecular mechanisms that underlie cisplatin resistance is of paramount importance, as it holds the key to enhancing therapeutic strategies and

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ultimately improving the prognosis and survival rates of ovarian cancer patients.[4] Cisplatin resistance in ovarian cancer arises from multifaceted processes, including multidrug resistance, DNA damage repair, metabolic reprogramming, oxidative stress, cell cycle dysregulation, cancer stem cell activity, immune modulation, apoptosis evasion, autophagy, and abnormal signaling pathways.[5] Consequently, no single pathway can fully account for the observed therapeutic resistance.

Inflammation is a key pathogenic driver in ovarian cancer. The process of ovulation triggers a localized inflammatory response, which may contribute to carcinogenesis. Although most ovarian cancers originate in the fallopian tubes, malignant cells subsequently implant onto the ovarian surface. Notably, the primary site of cancer cell dissemination is often not the ovary itself but adjacent peritoneal surfaces and surgical wound sites, where intense and persistent inflammatory responses promote tumor growth and invasion.[6] Chronic inflammation induces cellular damage, oxidative stress, and increased production of cytokines and prostaglandins, all of which can promote mutagenicity. Thus, inflammation plays a key role in the development of ovarian cancer.

The unique tumor microenvironment within ovarian cancer is characterized by several distinct factors, notably including hypoxia and inflammation.[7,8] Hypoxia, resulting from an inadequate oxygen supply in the microenvironment of solid tumors, has emerged as a pivotal player in the promotion of cancer progression and a key determinant in shaping the response to therapeutic interventions.[9] Recent studies have reported that suppressed glycolysis and increased oxidative metabolism in ovarian cancer cells can stimulate the production of pro-inflammatory mediators, potentially contributing to resistance to cisplatin therapy.[10] Concurrently, inflammatory signaling, mediated by cytokines and interleukins (ILs), influences tumor proliferation,[11] immune evasion,[12] and, most notably, drug resistance.[13] This complex interplay between hypoxia-induced stress and inflammatory signaling forms a dynamic backdrop within the landscape of ovarian cancer.[14-17] It introduces a new layer of complexity that intimately intersects with disease progression and the therapeutic efficacy of interventions.

Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) has been the subject of intensive scientific exploration due to its well-established role in host defense mechanisms against viral infections.[18] A wealth of prior research has unveiled *IFIT1* as an interferon (IFN)-inducible gene that exerts potent antiviral effects by impeding viral replication.[19-22] It functions as a guardian of the host cell,[23] shielding it from the intrusion of viral pathogens.[24,25] However, recent investigations have ventured into uncharted territory, suggesting that IFIT1's biological relevance may transcend its classical antiviral role.[26] Recent studies have demonstrated that *IFIT1* modulates hypoxia signaling pathways, influencing downstream genes involved in cell proliferation and apoptosis, thereby contributing to cancer initiation and progression.[27] Hypoxia is also a key driver of epithelial–mesenchymal transition, and alterations in its pathway components—across the cell membrane, cytoplasm, and nucleus—have been implicated in ovarian tumorigenesis.[28] The emerging evidence strongly suggests a broader impact, positioning *IFIT1* as a potential linchpin in the intricate machinery of cancer biology.[29-31] Particular attention has been drawn to its involvement in cancer, with an emphasis on its potential role in driving chemoresistance, particularly in the context of ovarian cancer.[32]

Here, we provide a comprehensive investigation into the multifaceted role of *IFIT1* in cisplatin resistance in ovarian cancer. The findings shed light on the molecular, functional, and clinical aspects of *IFIT1*'s involvement in cisplatin resistance, potentially opening new avenues for therapeutic strategies.

2. Materials and methods

2.1. Data collection

We obtained publicly available transcriptomic datasets from the Gene Expression Omnibus database of the National Center for Biotechnology Information, including five datasets: GSE58470, GSE47856, GSE66957, GSE18520, and GSE16708. The GSE58470 dataset was used to compare gene expression differences between cisplatin-sensitive and cisplatin-resistant ovarian cancer cells, thereby revealing transcriptomic reprogramming following prolonged cisplatin exposure. The GSE47856 dataset contains gene expression profiles of ovarian cancer cells before and after cisplatin treatment, simulating the acute transcriptional response to cisplatin stimulation. The GSE66957 dataset includes 57 ovarian cancer tissue samples and 12 normal ovarian tissue samples, which were used to assess differential expression of *IFIT1* between tumor and normal tissues. In addition, GSE18520 (53 ovarian cancer samples and 10 normal ovarian samples) and GSE16708 (17 ovarian cancer samples and nine normal ovarian samples) served as independent supplementary data sources to enhance the robustness of our results.

Differential expression analysis was performed using the *limma* package in R, with the thresholds set at $p<0.05$ and $|\log_2 FC| > 1.3$. To identify consistently dysregulated genes across datasets, Venn diagrams were constructed to screen for overlapping genes. Further analysis focused

on the key candidate gene *IFIT1*, whose transcriptional expression between normal and ovarian cancer tissues was visualized using the Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/). In addition, to validate the protein-level expression of IFIT1, we obtained immunohistochemical staining images from the Human Protein Atlas (https://www.proteinatlas.org/) and compared the staining intensity between normal ovarian tissues and ovarian cancer tissues.

Gene Set Enrichment Analysis (GSEA) was performed on RNA-seq data from 426 ovarian cancer samples from The Cancer Genome Atlas (TCGA) using the MSigDB hallmark gene sets, with thresholds set at FDR < 0.25 and $p<0.05$ to evaluate relevant signaling pathways. TCGA data, including RNA-seq and clinical information, were used to analyze IFIT1 expression and associated signaling pathways. RNA-seq data from the Genotype-Tissue Expression (GTEx) project were used to assess the tissue-specific expression of IFIT1 in normal tissues, and a combined analysis with TCGA data was performed to compare IFIT1 expression between tumor and normal tissues.

2.2. Cell culture

Ovarian cancer cell lines A2780 and OVCAR8 were obtained from the American Type Culture Collection (USA). Cisplatin-resistant A2780 cells (A2780/CP) were developed by gradually increasing cisplatin concentrations over several months. All cell lines were cultured in RPMI-1640 supplemented with 10% fetal bovine serum (Gibco, USA) and 1% penicillin–streptomycin (Sangon Biotech, USA). Hypoxia was induced by culturing the cells in a hypoxia chamber (Model 27310, StemCell, Canada) under conditions of 1% O_2, 5% CO_2, and 94% N_2 for 24 h. Cells were treated with 20 μM $CoCl_2$ (MERYER, China) or 10 μM LW6 (Aladdin, China) for 24 h to mimic hypoxia and inhibit hypoxia-inducible factor-1 alpha (HIF-1α) signaling, respectively.

2.3. RNA inhibition and real-time polymerase chain reaction (PCR)

The lentiviral vectors targeting human *IFIT1* and *HIF1A* were purchased from Sigma-Aldrich (USA). The target sequences of the short hairpin RNA (shRNA) constructs were as follows: *IFIT1*-shRNA1: 5'-GAGTTATCCATTGATGACGAT-3'; *IFIT1*-shRNA2: 5'-CGTCAATGCAATTATCCATTA-3'; *HIF1A*-shRNA1: 5'-CCGCTGGAGACACAATCATAT-3'; *HIF1A*-shRNA2: 5'-CCAGTTATGATTGTGAAGTTA-3'. Ovarian cancer cells were infected with lentiviral particles and selected with puromycin for seven days. Total RNA was reverse-transcribed using the SuperScript III First-Strand Synthesis System (Cat. No. 18080-051, Thermo Fisher Scientific, USA), followed by quantitative real-time PCR on a QuantStudio 6 Flex system (Thermo Fisher Scientific, USA) with PowerUp SYBR Green Master Mix (Cat. No. A25742, Thermo Fisher Scientific, USA). Primers for human *IFIT1* were as follows: forward 5'-TTGATGACGATGAAATGCCTGA-3' and reverse 5'-CAGGTCACCAGACTCCTCAC-3'. *GAPDH* served as the internal control, with primers: forward 5'-GGAGCGAGATCCCTCCAAAAT-3' and reverse 5'-GGCTGTTGTCATACTTCTCATGG-3'.

2.4. Luciferase activity and chromatin immunoprecipitation (ChIP) assays

The pNFκB-luc plasmid was purchased from Beyotime (China). The promoter region of the human *IFIT1* gene was amplified from genomic DNA of A2780 cells and cloned into the pGL4.15 vector (Promega, USA). After transfection, cells were lysed, and luciferase activity was measured using the Dual Luciferase Assay System (E1960, Promega, USA). Luciferase activity was normalized to Renilla luciferase.

For the ChIP assay, cells were cross-linked with formaldehyde (Sangon Biotech, China) to preserve protein–DNA interactions. The cross-linked chromatin was sheared by sonication into fragments of 100–500 base pairs. After centrifugation, the supernatant containing sheared chromatin was incubated overnight at 4°C with antibodies against HIF-1α or with normal IgG as a control. This procedure allows specific immunoprecipitation of protein–DNA complexes for subsequent analysis.

2.5. Western blot

Cells were harvested and lysed using sodium dodecyl sulfate (SDS) lysis buffer (Beyotime, China). Equal amounts of protein from each sample were separated using SDS-polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes (Beyotime, China). After blocking with 5% non-fat milk for 1 h, the membranes were incubated overnight at 4°C with the appropriate primary antibodies. After washing using phosphate-buffered saline with Tween-20, membranes were exposed to the secondary antibody for 1 h at room temperature. Protein signals were then detected using an enhanced chemiluminescence kit (32106, Thermo Scientific, China), with β-actin as the internal loading control. The primary antibodies (A0366, ABclonal, China) used were: anti-IFIT1 (ab70023, Abcam, UK), anti-HIF-1α (20960-1-AP, Proteintech, USA), and anti-β-actin (sc-8432, Santa Cruz, USA).

2.6. Cell viability, clonogenic formation, and Caspase3/7 activity assays

Cell viability was measured with the Cell Counting Kit-8 (CCK-8; CK04, Dojindo, Japan). Cells were seeded in

96-well plates at a density of 1×10^4 cells per well and treated with cisplatin (TargetMol, China). After 48 h, 10 μL of CCK-8 reagent was added to each well, followed by incubation for 2 h, after which absorbance was measured at 450 nm.

For clonogenic formation assays, cells were seeded in 6-well plates at a density of 1×10^5 cells per well and treated with cisplatin. After 14 days, colonies were fixed and stained with crystal violet (ZeYe, China). Colonies containing more than 50 cells were counted.

Caspase-3/7 activity was measured using the Caspase-Glo 3/7 Assay (G8981, Promega). Cells were treated with cisplatin, and luminescence was measured using a microplate reader (BioTek Synergy Neo2, Agilent, United States of America [USA]).

2.7. Statistical analysis

Data were analyzed with GraphPad Prism 9 (GraphPad Software, USA). Statistical comparisons were conducted using two-tailed unpaired *t*-tests, one-way analysis of variance, and log-rank tests,[33] with $p<0.05$ as the threshold for significance. Experiments were conducted in triplicate, and results are shown as mean ± standard deviation.

3. Results

3.1. Transcriptome profiling identifies IFIT1 as a key regulator of cisplatin resistance in ovarian cancer cells

To elucidate the molecular mechanisms underlying cisplatin resistance in ovarian cancer cells, we conducted transcriptomic analyses on cisplatin-sensitive and cisplatin-resistant cell lines. Long-term cisplatin exposure resulted in 426 upregulated and 502 downregulated genes (Figure 1A and B). Short-term cisplatin treatment induced 21 upregulated and three downregulated genes (Figure 1C and D). GSEA revealed that long-term cisplatin resistance was associated with activation of apoptosis, DNA damage repair, hypoxia, and inflammatory pathways, whereas myogenesis and the mTOR pathway were suppressed. In contrast, short-term cisplatin treatment activated epithelial–mesenchymal transition, hypoxia, and inflammatory pathways, with distinct inhibition patterns compared to long-term resistance (Figure 1E).

These findings suggest that hypoxia and inflammatory pathways are features of cisplatin resistance in ovarian cancer cells. Overlapping analysis of genes upregulated in both short-term treatment and long-term resistance identified *IFIT1* as the sole common gene (Figure 1F). Real-time PCR confirmed elevated *IFIT1* expression in cisplatin-resistant A2780/CP cells (Figure 1G), and cisplatin treatment induced *IFIT1* expression in A2780 cells (Figure 1H). Consistently, analysis of public transcriptome datasets demonstrated significantly higher *IFIT1* expression in A2780/CDDP cells compared with A2780 cells in GSE206649, and in resistant PEA2 and PEO4 cell lines in GSE149146. Western blot analysis further validated elevated IFIT1 protein levels in resistant cells (Figure S1).

Collectively, these results indicate that *IFIT1* plays a critical role in cisplatin resistance in ovarian cancer and suggest that it may serve as a central hub driving the acquisition of resistance.

3.2. IFIT1 promotes cisplatin resistance in ovarian cancer cells

To functionally assess the role of IFIT1 in cisplatin resistance in ovarian cancer cells, we established stable *IFIT1*-knockdown cell lines in A2780/CP cells using two distinct shRNA sequences, both of which effectively suppressed *IFIT1* expression (Figure 2A and B, Figure S3). Knockdown of *IFIT1* significantly reduced cell viability after cisplatin treatment (Figure 2C) and markedly decreased colony formation compared to control cells (Figure 2D and E). Caspase-3/7 activity assays showed increased apoptotic activity in *IFIT1*-knockdown cells following cisplatin treatment (Figure 2F). Expanding our investigation, we established stable cell lines in OVCAR8 that either overexpressed an empty vector or IFIT1 (Figure 2G). Compared to knockdown of *IFIT1*, stable overexpression of *IFIT1* in OVCAR8 cells resulted in increased cell viability (Figure 2H) and colony formation (Figure 2I and J) after cisplatin exposure, accompanied by decreased caspase-3/7 activity (Figure 2K). These results provide strong functional evidence that *IFIT1* contributes to cisplatin resistance in ovarian cancer cells, highlighting it as a potential therapeutic target for overcoming chemoresistance.

3.3. IFIT1 is associated with multiple inflammatory pathways in ovarian cancer

To investigate the molecular mechanisms by which *IFIT1* contributes to cisplatin resistance in ovarian cancer, we performed GSEA using RNA-seq data from 426 ovarian cancer samples from TCGA. Our analysis confirmed that *IFIT1* expression was associated with the activation of IFN pathways, including IFN-α (Figure 3A) and IFN-γ (Figure 3B), consistent with its role as an IFN-inducible gene. Notably, our analysis unveiled a broader involvement of IFIT1 in inflammatory signaling pathways. High *IFIT1* expression showed a significant positive correlation with multiple inflammatory pathways, including IL2/signal transducer and activator of transcription (STAT) 5 (Figure 3C), IL6/STAT3 (Figure 3D), tumor

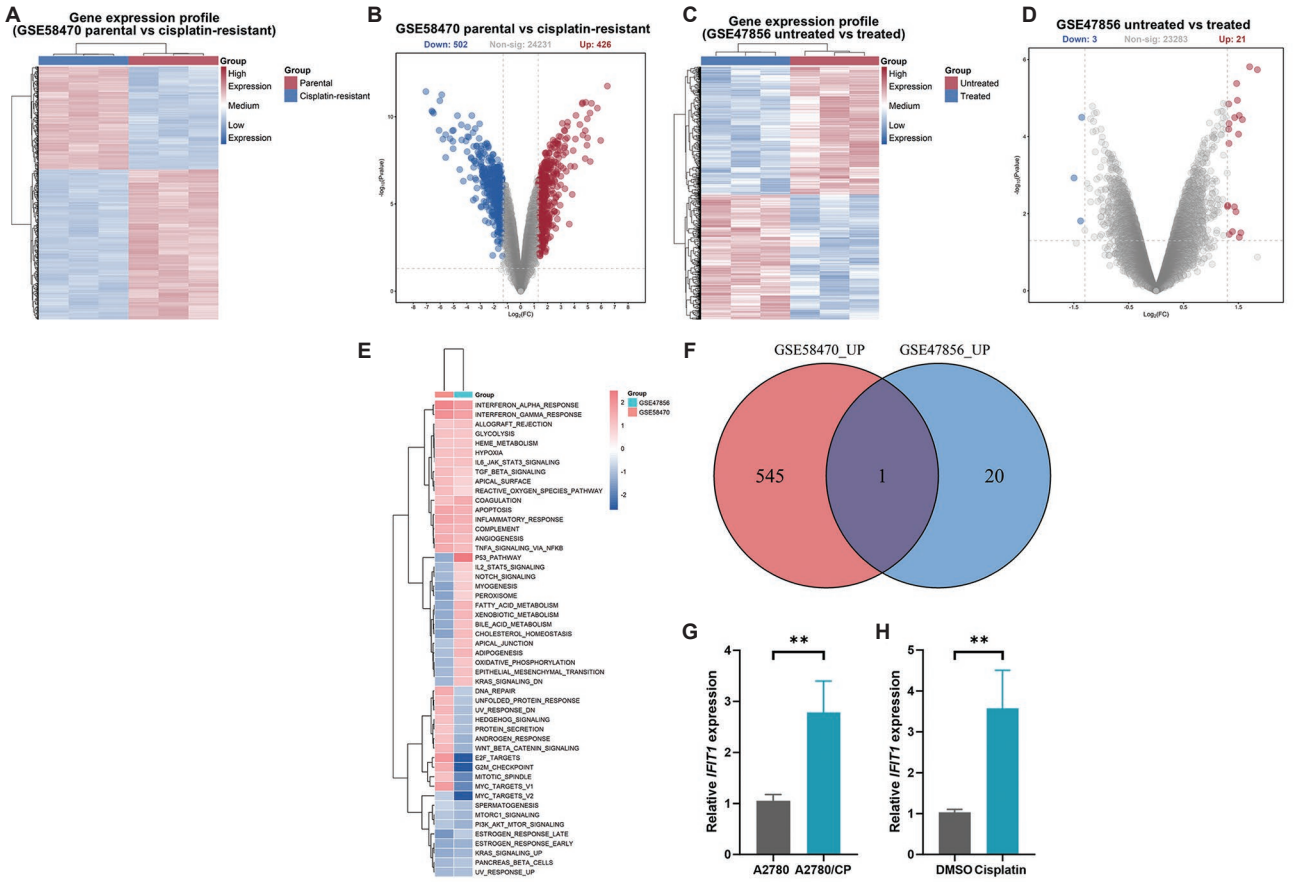

Figure 1. Transcriptome profiling reveals altered gene expression in cisplatin-resistant ovarian cancer cells. (A) Heatmap displaying differentially expressed genes in long-term cisplatin-resistant ovarian cancer cells compared to cisplatin-sensitive cells. (B) Volcano plot illustrating significantly upregulated (red) and downregulated (blue) genes in long-term cisplatin-resistant cells based on $|Log_2FC| > 1.3$ and false discovery rate (FDR) < 0.05 thresholds. (C) Heatmap representing differentially expressed genes in ovarian cancer cells after short-term cisplatin exposure. (D) Volcano plot displaying significant upregulated (red) and downregulated (blue) genes in cells subjected to short-term cisplatin treatment. Genes with |Log2FC| > 1.3 and FDR < 0.05 were considered significantly differentially expressed. (E) Comparison of signaling pathways activated in long-term cisplatin-resistant cells and cells exposed to short-term cisplatin treatment. (F) Identification of interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) as a common upregulated gene in both long-term cisplatin-resistant and short-term cisplatin-treated cells. (G) Real-time polymerase chain reaction validation of increased *IFIT1* expression in A2780/CP cells with cisplatin resistance ($n = 3$, $^{**}p<0.01$ vs. A2780). (H) Induction of *IFIT1* expression in A2780 cells by cisplatin ($n = 3$, $^{**}p<0.01$ vs. dimethyl sulfoxide).

necrosis factor alpha signaling (Figure 3E), and a general inflammatory response (Figure 3F). These associations were further validated by correlation analyses across the TCGA dataset, which demonstrated a strong positive relationship between *IFIT1* expression and activation of these signaling pathways (Figure S2). Previous research has documented autocrine production of ILs and cytokines in ovarian cancer, with IL signaling implicated in cisplatin resistance.[34] To delve further into these findings, we examined IL6 and IL8 mRNA levels in *IFIT1*-knockdown A2780 cells and observed reduced expression of both cytokines (Figure 3G), accompanied by decreased activation of nuclear factor kappa-B (NF-κB) signaling (Figure 3H). Conversely, *IFIT1* overexpression in OVCAR8 cells enhanced NF-κB activation and increased IL6 and IL8 expression (Figure 3I and J). Collectively, these results substantiate the notion that IFIT1 is closely associated with the activation of multiple inflammatory pathways in ovarian cancer, supporting its potential role in promoting cisplatin resistance.

3.4. High *IFIT1* expression predicts poor prognosis in ovarian cancer

A comprehensive analysis of *IFIT1* expression in ovarian cancer was conducted using datasets from TCGA, the GTEx project, and GEPIA. *IFIT1* was markedly upregulated in 426 ovarian cancer tissues compared to 88 normal ovarian tissues (Figure 4A). This observation was further validated in three independent GEO cohorts (GSE66957, GSE18520, and GSE16708), which consistently

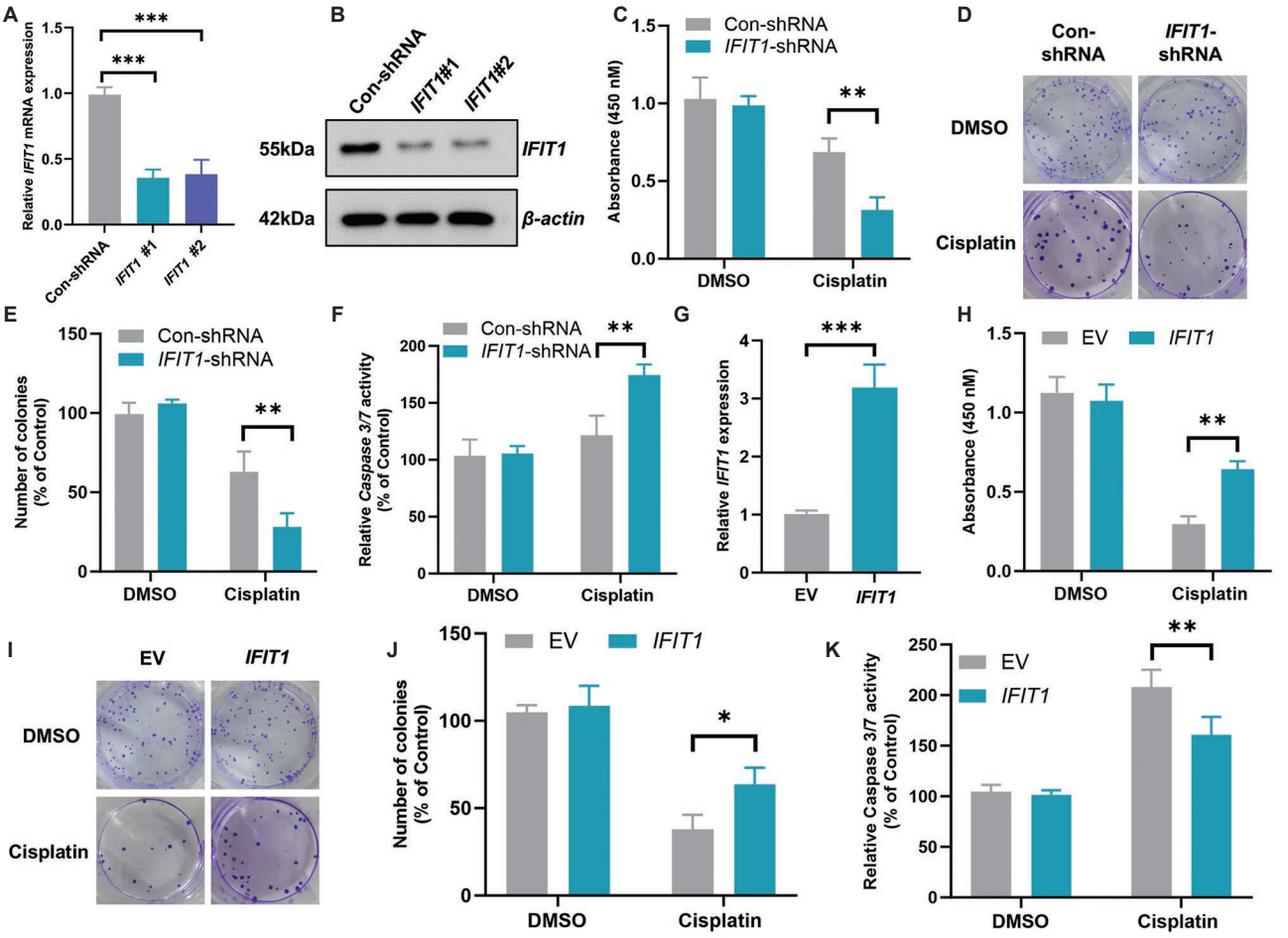

Figure 2. Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) mediates cisplatin resistance in ovarian cancer cells. (A) Knockdown of *IFIT1* using two distinct shRNA sequences in A2780/CP cells (n = 3, ***p<0.001 vs. Con-shRNA). (B) Effective reduction of IFIT1 protein levels upon shRNA-mediated knockdown (n = 3). (C) Cell viability assay (Cell Counting Kit-8) showing increased sensitivity to cisplatin in *IFIT1*-knockdown cells (n = 3, **p<0.01 vs. Con-shRNA). (D) Clonogenic formation assay demonstrating a decrease in colony formation in *IFIT1*-knockdown cells. (n = 3). (E) Quantification of the clonogenic formation assay of the cells from (D) (n = 3, **p<0.01 vs. Con-shRNA). (F) Caspase3/7 activity assay indicating elevated apoptosis in *IFIT1*-knockdown cells after cisplatin treatment (n = 3, **p<0.01 vs. Con-shRNA). (G) Stable overexpression of *IFIT1* in OVCAR8 cells (***p<0.001 vs. EV). (H) Enhanced cell viability in OVCAR8 cells overexpressing *IFIT1* following cisplatin treatment (n = 3). (I) Increased colony formation in OVCAR8 cells overexpressing *IFIT1* (n = 3). (J) Quantification of the clonogenic formation assay of the cells from (I) (n = 3, *p<0.05 vs. EV). (K) Reduced caspase3/7 activity in *IFIT1*-overexpressing OVCAR8 cells after cisplatin treatment. (n = 3, **p<0.01 vs. EV).
Abbreviations: DMSO: Dimethyl sulfoxide; EV: Empty vector; shRNA: Short hairpin RNA.

demonstrated elevated *IFIT1* mRNA expression in ovarian cancer tissues relative to normal controls (Figure 4B-D). To corroborate these findings at the protein level, we analyzed immunohistochemistry data from the Human Protein Atlas (http://www.proteinatlas.org/), which revealed significantly increased IFIT1 protein staining in ovarian cancer tissues compared to normal ovarian tissues (Figure 4E).

To assess the clinical relevance of IFIT1, we evaluated its association with patient prognosis using Kaplan–Meier Plotter (https://kmplot.com/). High IFIT1 expression was significantly associated with reduced overall survival (Figure 4F), progression-free survival (Figure 4G), and post-progression survival (Figure 4H).

Collectively, these findings indicate that elevated *IFIT1* expression significantly correlates with an unfavorable prognosis in ovarian cancer patients.

3.5. *IFIT1* is a transcriptional target of HIF-1α in ovarian cancer

Given the established role of hypoxia in ovarian cancer progression and cisplatin resistance, we examined whether hypoxia governs *IFIT1* expression. *IFIT1* mRNA expression showed a strong positive correlation with HIF-1α

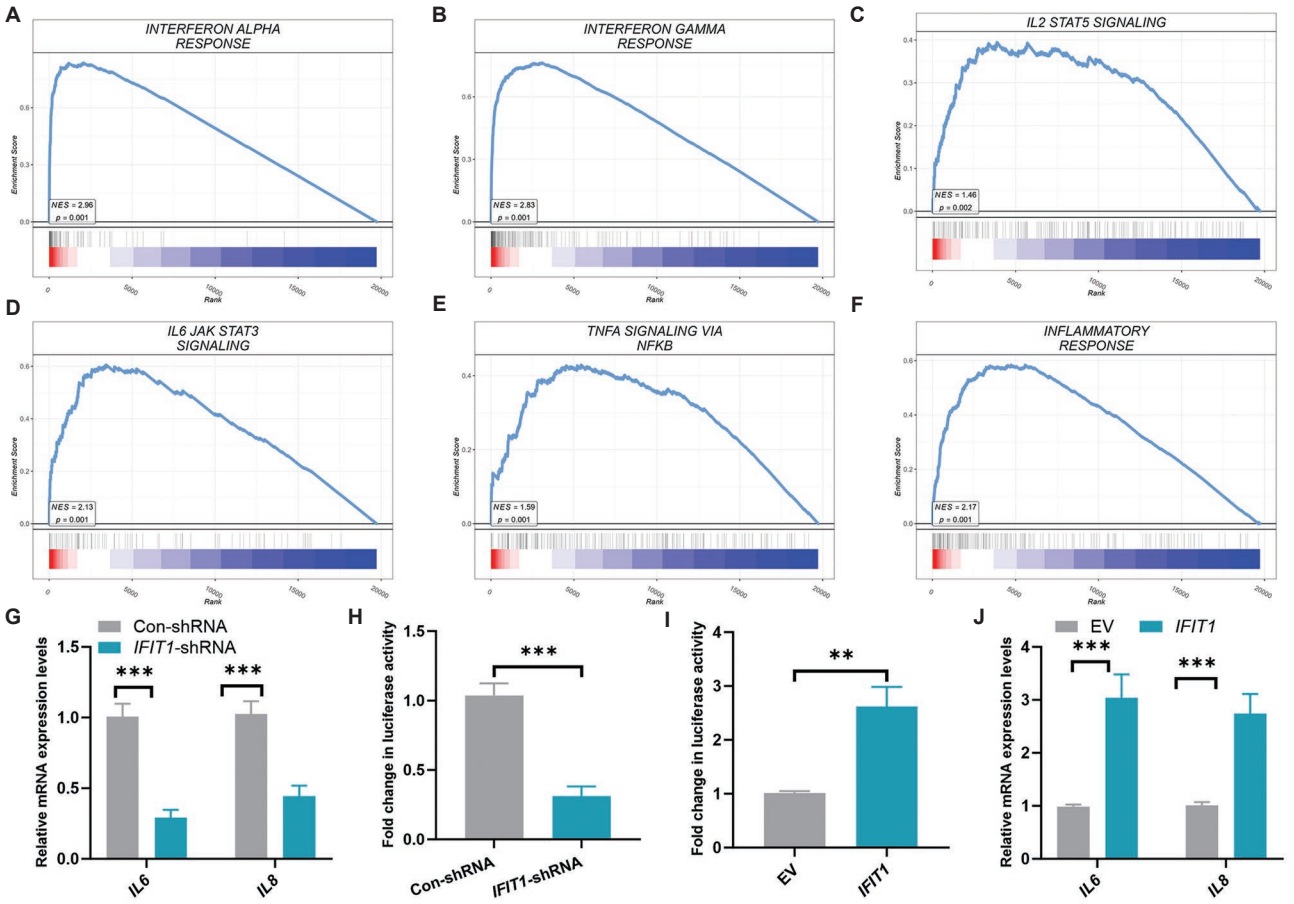

Figure 3. Interferon-induced protein with tetratricopeptide repeats 1 (*IFIT1*) is associated with activation of multiple inflammatory pathways in ovarian cancer. (A) Activation of the interferon-alpha pathway in ovarian cancer samples with elevated *IFIT1* expression. (B) *IFIT1* expression correlates with the activation of the interferon-gamma pathway. (C) Positive correlation between *IFIT1* expression and IL2_STAT5 pathway activation. (D) IL6_STAT3 pathway activation in ovarian cancer samples with increased *IFIT1* expression. (E) Enhanced TNFα pathway activation in the presence of elevated *IFIT1* expression. (F) Broader inflammatory response enriched in ovarian cancer samples with high *IFIT1* expression. (G) Reduced IL6 and IL8 mRNA levels in *IFIT1*-knockdown A2780 cells (n = 3, ***p<0.001 vs. Con-shRNA). (H) Dampening of NF-κB signaling activation in *IFIT1*-knockdown A2780 cells (n = 3, ***p<0.001 vs. Con-shRNA). (I) Activation of NF-κB signaling in A2780 cells overexpressing *IFIT1* (n = 3, **p<0.01 vs. EV). (J) Increased IL6 and IL8 mRNA levels in A2780 cells overexpressing *IFIT1* (n = 3, ***p<0.001 vs. EV).
Abbreviations: EV: Empty vector; NES: Normalized enrichment score; NF-κB: Nuclear factor kappa-B; shRNA: Short hairpin RNA; IL: Interleukin.

(Figure 5A), but not with HIF-2α (Figure 5B), indicating a specific association between *IFIT1* and HIF-1α signaling in ovarian cancer. To delve deeper, A2780 and OVCAR8 cells were exposed to hypoxic conditions or treated with the hypoxia mimic $CoCl_2$, both of which significantly increased *IFIT1* expression (Figure 5C and D). Silencing HIF-1α expression with two distinct shRNAs led to a decrease in *IFIT1* expression (Figure 5E). Furthermore, treatment of A2780 cells with the HIF-1α inhibitor LW6 effectively suppressed both basal and cisplatin-induced *IFIT1* expression (Figure 5F). Promoter analysis of the human *IFIT1* gene revealed two canonical hypoxia response elements (HREs) (Figure 5G). We generated luciferase reporter constructs containing either both, one, or none of these HREs (Figure 5H). Luciferase assays confirmed that HIF-1α significantly enhanced the transcriptional activity of the wild-type *IFIT1* promoter. Mutation of one HRE partially reduced promoter activity, whereas mutation of both HREs completely abolished it (Figure 5I). ChIP assays further demonstrated that HIF-1α directly binds to the *IFIT1* promoter (Figure 5J).

These findings provide compelling evidence that *IFIT1* is a direct transcriptional target of HIF-1α in ovarian cancer, underscoring the intricate regulatory role of HIF-1α in cisplatin-induced *IFIT1* expression.

4. Discussion

This study identifies *IFIT1* as a pivotal mediator of cisplatin resistance in ovarian cancer, bringing to light new insights

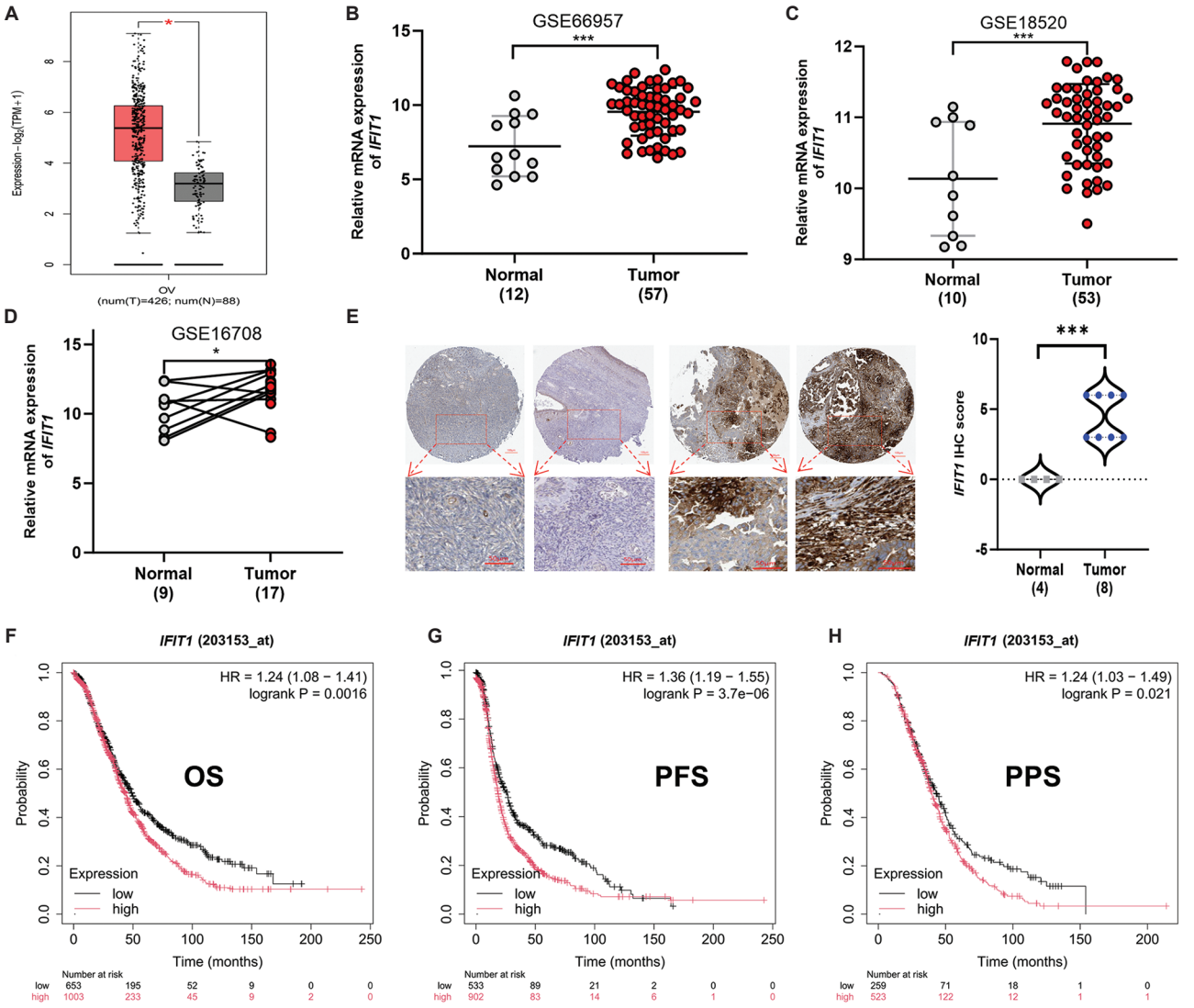

Figure 4. High interferon-induced protein with tetratricopeptide repeats 1 (*IFIT1*) expression predicts poor prognosis in ovarian cancer. (A) Increased *IFIT1* mRNA expression in ovarian cancer tissues compared to normal ovarian tissues (*p<0.05 vs. Normal). (B-D) Consistent upregulation of *IFIT1* mRNA in ovarian cancer tissues across multiple independent cohorts (***p<0.001 vs. Normal, *p<0.05 vs. Normal). (E) Immunohistochemistry illustrating elevated *IFIT1* protein staining in ovarian cancer tissues relative to normal ovarian tissues (***p<0.001 vs. Normal). Scale bars: 50 μm. (F-H) Correlation between higher *IFIT1* expression and reduced overall survival, progression-free survival, and post-progression survival in ovarian cancer patients.

into both its clinical significance and underlying molecular mechanisms. Transcriptome profiling of cisplatin-sensitive and cisplatin-resistant cells consistently demonstrated that *IFIT1* is significantly upregulated in long-term resistant cell lines as well as in cells subjected to short-term cisplatin exposure, establishing *IFIT1* as a key driver of chemoresistance. Functional assays further validated this role, as *IFIT1* knockdown enhanced cisplatin sensitivity, whereas *IFIT1* overexpression promoted resistance, underscoring its functional importance in modulating therapeutic response.

In addition to its role in drug resistance, our findings reveal a strong linkage between *IFIT1* expression and inflammatory signaling pathways, which are known to contribute to tumor progression and chemoresistance in ovarian cancer.[35] This suggests that *IFIT1* may serve as an upstream activator of these pathways, adding another layer of complexity to the regulatory mechanisms underlying cisplatin resistance.

The clinical relevance of *IFIT1* is further supported by analyses of patient datasets, which consistently show

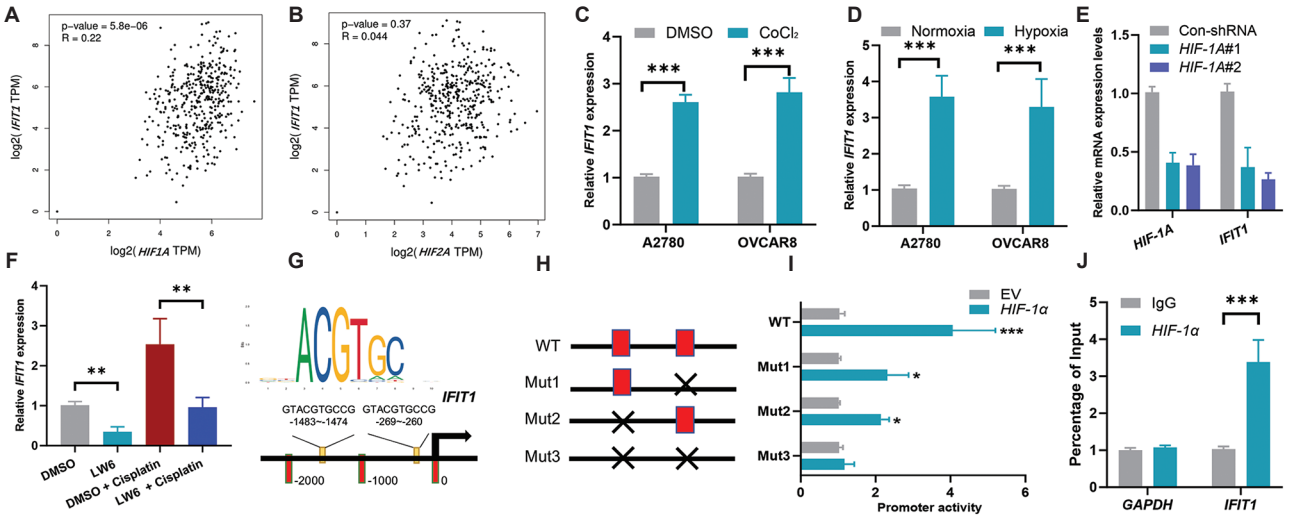

Figure 5. Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) is a transcriptional target of hypoxia-inducible factor-1 alpha (HIF-1α) in ovarian cancer. (A) Correlation between *IFIT1* mRNA expression and HIF-1α in ovarian cancer samples. (B) No significant correlation observed between *IFIT1* expression and HIF-2α. (C) Induction of *IFIT1* expression in both A2780 and OVCAR8 cells under $CoCl_2$-mimic hypoxia conditions (n = 3, ***p<0.001 vs. DMSO). (D) Induction of *IFIT1* expression in both A2780 and OVCAR8 cells under hypoxia conditions (n = 3, ***p<0.001 vs. Normoxia). (E) Reduced *IFIT1* expression upon HIF-1α silencing in A2780 cells (n = 3, ****p<0.0001 vs. Con-shRNA). (F) Inhibition of *IFIT1* expression by the HIF-1α inhibitor LW6 in A2780 cells treated with or without cisplatin (n = 3, **p<0.01 vs. DMSO). (G) Identification of two hypoxia response elements (HREs) in the *IFIT1* promoter region. (H) Human *IFIT1* promoter contains two potential HREs (highlighted in red). Mutant sites are marked with a cross. (I) The effect of HIF-1α on luciferase activity of wild-type IFIT1 and mutant promoters (n = 3, ***p<0.001 vs. EV, *p<0.05 vs. EV). (J) ChIP-qPCR assay showed the enrichment of HIF-1α in the putative HIF-1α binding site of the *IFIT1* promoter region (n = 3, ***p<0.001 vs. IgG).
Abbreviations: DMSO: Dimethyl sulfoxide; EV: Empty vector; shRNA: Short hairpin RNA; ChIP: Chromatin immunoprecipitation; qPCR: Quantitative polymerase chain reaction; IgG: Immunoglobulin G.

that high *IFIT1* expression is associated with unfavorable prognosis across multiple independent cohorts. These findings accentuate the potential of *IFIT1* as a prognostic biomarker and warrant further exploration of its clinical applications. Moreover, our study elucidates the transcriptional regulation of *IFIT1* by HIF-1α, unveiling its integration into the hypoxia response, a well-established contributor to chemoresistance. This mechanistic insight further deepens our understanding of the intricate network of pathways involved in cisplatin resistance.

While our study provides significant advances by identifying IFIT1 as a key mediator of cisplatin resistance in ovarian cancer, several limitations should be acknowledged. The findings are primarily based on cell-based experiments and bioinformatics analyses, and thus necessitate further validation through *in vivo* models and clinical studies. In addition, cisplatin resistance involves a multifactorial network of signaling pathways, many of which remain incompletely characterized. Therefore, further mechanistic studies are warranted to fully delineate the role of IFIT1 within this network. Finally, the translation of IFIT1-targeted strategies into clinical applications will necessitate rigorous preclinical evaluation to assess efficacy, safety, and therapeutic feasibility.

5. Conclusion

This study demonstrates that *IFIT1* is markedly upregulated in ovarian cancer and plays a pivotal regulatory role in mediating cisplatin resistance. Knockdown of *IFIT1* significantly reduces cellular resistance to cisplatin, suppresses cell viability and clonogenic capacity, and promotes apoptosis. Mechanistically, elevated *IFIT1* expression activates multiple inflammation-related signaling pathways, with IL-associated pathways likely playing a central role in driving cisplatin resistance. Furthermore, we identified the hypoxic tumor microenvironment as a key regulator of *IFIT1* expression. Preliminary analyses revealed a strong positive correlation between *IFIT1* mRNA levels and HIF-1α, and subsequent experiments confirmed that *IFIT1* is a direct transcriptional target of HIF-1α in ovarian cancer.

Collectively, these findings provide new insights into the molecular basis of cisplatin resistance in ovarian cancer. The identification of *IFIT1* highlights its critical role in driving chemoresistance and suggests that it may represent a promising target for the development of personalized therapeutic strategies. Potential IFIT1-directed interventions may include small-molecule

inhibitors, monoclonal antibodies, or RNA interference technologies (e.g., siRNA or shRNA) designed to enhance cisplatin sensitivity and overcome resistance. In addition, targeting the HIF-1α/IFIT1 signaling axis may offer an indirect yet promising strategy that warrants further investigation.

Despite these advances, several limitations should be acknowledged. Functional validation in this study relied on a single shRNA construct, which may pose a risk of off-target effects. Future studies should incorporate multiple independent shRNA constructs or CRISPR/Cas9-mediated gene editing for rigorous cross-validation, alongside complementary experimental approaches to ensure phenotype specificity. In addition, although IFIT1-targeted therapy shows promising potential, its safety profile, *in vivo* efficacy, and interactions with the tumor immune microenvironment remain to be systematically evaluated. These efforts will be indispensable for advancing IFIT1-based therapies toward clinical translation and ultimately improving therapeutic outcomes and survival in patients with ovarian cancer.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: All authors
Investigation: All authors
Methodology: All authors
Writing–original draft: All authors
Writing–review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

All data generated or analyzed during this study are included in this published article.

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