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Original Research

HELQ upregulates PARP1 to drive platinum resistance and predict therapeutic response in ovarian cancer

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ABSTRACT

POLQ-like helicase (HELQ), an evolutionarily conserved 3'-5′ DNA helicase, is markedly overexpressed in platinum-resistant ovarian cancer (OC), which is correlated with a poor prognosis. However, the mechanisms linking HELQ with resistance to platinum-based chemotherapy remain unkonwn. Our study presents both *in vitro* and *in vivo* evidence that elevated HELQ expression is linked to increased chemoresistance in OC models, with reduced HELQ levels enhancing their sensitivity to platinum agents. The expression of γH2AX, RPA1 and 53BP1 determined by immunofluorescence and western blot indicated that HELQ could promote platinum-induced DNA damage repair. HELQ was found to promote OC platinum resistance by regulating the expression of poly (ADP-ribose) polymerase 1(PARP1), which could be reversed by PARP1 downregulation. Furthermore, *in vitro* experiments showed that HELQ overexpression sensitizes OC cells to PARP inhibitors (PARPi). Immunohistochemical analysis indicates that diminished HELQ expression in tumor tissues correlates with disease progression in patients with first-line maintenance therapy with PARPi, whereby higher expression levels predict improved progression-free survival. Notably, we found a positive correlation between PARP1 and HELQ expression. In conclusion, HELQupregulats PARP1 to promote platinum resistance in OC and warrants consideration as an emerging biomarker for monitoring therapeutic responses to chemotherapy and PARPi treatment in ovarian cancer.

Introduction

Ovarian cancer (OC) stands out as the most fatal gynecological malignancy, with the annual global death toll exceeding 207,000, while also ranking eighth in mortality among all cancerin women [1]. Adjuvant chemotherapy preceded by primary debulking surgery combined with platinum-based chemotherapy has become the standard of treatment for OC in recent years [2]. However, most patients are diagnosed at a late stage and the development of resistance to platinum over the course of chemotherapy is nearly ubiquitous contributing to the poor prognosis of OC patients [3,4]. Although the advent of bevacizumab and poly ADP ribose polymerase (PARP) inhibitors (PARPi) has expanded the therapeutic arsenal for OC, the mortality rate remains distressingly high [5]. Thus, it is urgent to elucidate the mechanisms of platinum resistance and identify novel biomarkers capable of gauging the responsiveness to therapeutic interventions in ovarian cancer.

Platinum compounds represent a cornerstone of chemotherapy, exerting their antitumor effects primarily through the disruption of DNA structure and function [6]. The emergence of resistance to platinum drugs is often attributed to the dysregulated activation of DNA damage

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repair mechanisms, a phenomenon that can be particularly problematic in cancer treatment [7,8]. The DNA damage repair system encompasses a multitude of pathways, including Base Excision Repair (BER), Nucleotide Excision Repair (NER), Mismatch Repair (MMR), and Homologous Recombination Repair (HRR), each offering potential avenues for the identification of novel therapeutic targets that counteract platinum resistance [9,10].

POLQ-like helicase (HELQ), a highly conserved 3′−5′ DNA helicase, plays an important role in DNA replication and damage repair [11,12]. HELQ can act on stalled replication forks in the early stage of the homologous recombination repair process, while also being involved in the repair of DNA interstrand crosslinks (ICLs) [13]. During the process, HELQ can directly bind to BCDX2, a collateral homologous compound of RAD51, to promote HRR at damaged replication forks [14]. In addition, HELQ along with ATR, RPA2, and BCDX2 can interact with the FANCD2/FANCI heterodimer, participating in the repair of DNA ICLs dependent on the FA pathway [15]. Liu DN et al. found that HELQ can participate in DNA damage repair through the CHK1-RAD51 pathway and reduce the sensitivity of osteosarcoma cells to chemotherapy [16]. Our previous studies revealed a significant correlation of HELQ expression, either in tumor tissues or ascites tumor cells, with the response to platinum-based chemotherapy as well as the prognosis of OC patients [17,18]. Despite these findings, the underlying mechanism through which HELQ confers chemoresistance in OC has yet to be fully elucidated.

In this study, we delineated a novel role for HELQ in modulating the chemoresistance of ovarian cancer cells through the regulation of PARP1 expression. Moreover, HELQ expression was highly correlated with the response to PARPi first-line maintenance treatments in OC patients. These findings yield new insights into the mechanisms of chemoresistance in ovarian cancer and may inspire new protocols for monitoring the response to chemotherapy and PARPi treatment in ovarian cancer.

Materials and methods

Cell culture

Human ovarian cancer cell lines (A2780, HeyA8, Hey, SKOV3, ES-2 and TOV112D) were purchased from the American Type Culture Collection (ATCC). Except for the ES-2 line, which was maintained in RPMI-1640 medium, all other cell lines were cultivated in DMEM medium enriched with 10 % fetal bovine serum. All cell lines were cultured in a humidified incubator within 5 % CO2 at 37 °C, authenticated by short tandem repeat (STR) profiling and confirmed to be mycoplasma-negative.

Cell transfection

To establish stable cell lines with downregulated or overexpressed HELQ, A2780 and HeyA8 cells in 6-well plates were transfected with lentivirus vectors encoding shHELQ and control vector or Flag and Flag-HELQ according to the manufacturer's instructions (GenePhama, China). At 48 h post-transfection, cells were cultured in medium with 2 ug/ml Puromycin for selection, resulting in theHeyA8 Flag, HeyA8 Flag-HELQ, A2780 shNC, and A2780 shHELQ-1/2 cell lines. (see Table S1 for sequences).

Western blot (WB) analysis

Cellular protein extraction was carried out using the NP40 lysis buffer (Beyotime Biotechnology, China), supplemented with a cocktail of proteinase inhibitors (APExBIO, USA). The lysate was clarified by centrifugation at 12,500 g for 15 min, and protein concentrations were determined using the BCA assay kit (Beyotime Biotechnology, China). Western blot was performed according to established protocols [19], with specific antibodies listed in Table S3. Each WB experiment was repeated three times to ensure the accuracy and consistency of results.

Bioinformatic analysis

The public Gene Expression Omnibus (GEO) datasets were utilized to assess the expression patterns of HELQ within ovarian cancer tissues. Additionally, an in-depth analysis of the correlation between *HELQ* and *PARP1* expression was performed using the GEPIA2 platform (http://gepia.cancer-pku.cn/) [20], which is based on data from The Cancer Genome Atlas (TCGA).

In vivo xenograft studies

Animal studies were performed according to protocols approved by the Animal Ethics Committee of Xiangya Hospital, Central South University. Nude mice (female, 6-week old, Beijing Hua Fukang Biological Polytron Technologies, Inc) were subcutaneously injected with 5×10^6 A2780 shNC or A2780 shHELQ cells. When the tumor size reached 100–150 mm^3, the mice were randomly divided into two groups and administered cisplatin(5mg/kg) or PBS by intraperitoneal injection twice a week. Tumors were measured by blinded staff, and volumes were calculated using the formula (length × widthˆ2) / 2 (mm^3).

Patients' tissue specimens

In the present study, paraffin-embedded surgical specimens from 55 patients who underwent surgery following first-line PARPi treatments at our hospital from 2020 to 2023 were analyzed. All patients were pathologically diagnosed with primary ovarian cancer and did not have other malignant diseases. The pathological characteristics of the patients are summarized in Table 1. Patients with a follow-up period of more than six months were included in the survival analysis. Progression-free survival (PFS) was defined as the time from surgery to the first observation of tumor recurrence. The protocol for the human study was reviewed and approved by the Ethics Committee of Xiangya Hospital, and the study was approved by the Ethics Committee of Xiangya Hospital, Central South University (NO.2017068222). Informed consent was obtained from all patients.

Statistical analysis

All statistical analyses were conducted using GraphPad Prism version 8.0.1 (GraphPad Software, Inc., La Jolla, *CA*, USA). Student's *t*-test was applied to discern significant differences between two groups. For comparisons involving three or more groups, one-way ANOVA complemented with Tukey's post hoc test for multiple comparisons was utilized. Assessments of correlation were based on Spearman's rank correlation coefficients. Survival data were analyzed using the log-rank test or the Mantel-Cox test, as appropriate. Associations between HELQ expression and clinical pathological parameters were evaluated using the Chi-square test or Fisher's exact test, where applicable. Differences with $P < 0.05$ were considered significant.

Results

HELQ promotes chemoresistance in OC

Our previous research revealed that HELQ expression levels in ovarian cancer tissues and ascites tumor cells are associated with platinum resistance [17,18]. Building upon these findings, we initially assessed HELQ expression across a panel of commercial OC cell lines, as depicted in supplementary Figs. 1A-B. At the same time, the IC50 values of cisplatin in OC cell lines were measured (Fig.S1C). After finding high expression in A2780 and low expression in HeyA8 cells, HELQ-downregulated cell lines (A2780 shHELQ-1/shHELQ-2) as well as

Table 1
The clinical characteristics of ovarian cancer patients with PARPi (Olaparib & Niraparib) in first-line maintenance.

Characteristics	low HELQ	high HELQ	*P value* (Chi-square/Fish's exact test)
Age			
≥55	17	11	0.227
<55	12	15	
BRCA status			
mutation	19	16	0.7594
wild type	10	10	
Histological type			
HGSOC	27	26	0.4923
non-HGSOC	2	0	
FIGO			
I-III	20	23	0.1078
IV	9	3	
Type of PARPi			
Olaparib	18	14	0.5371
Niraparib	11	12	
Primary CA125			
<=ULN	0	0	>0.9999
>ULN	29	26	
NACT			
Yes	8	3	0.1848
No	21	23	
Type of surgery			
PDS	20	23	0.1078
IDS	9	3	
Residual disease			
R0	16	18	0.284
>R0	13	8	
Response to chemotherapy			
CR	23	22	0.7329
PR	6	4	
Bevacizumab			
Yes	1	1	0.9373
No	28	25	

FIGO: the International Federation of Gynecology and Obstetrics; HGSOC: High-grade serous ovarian cancer; ULN: upper limit of the normal range; NACT: Neoadjuvant chemotherapy; PDS: primary debulking surgery; IDS: interval debulking surgery; CR: complete response; PR: partial response.

overexpressing cell lines (HeyA8 Flag-HELQ) and their controls (A2780 shNC, HeyA8 Flag) were constructed (Fig.S1D-E). To confirm the impact of HELQ on platinum resistance, these OC cells lines were treated with cisplatin for 48.h Based on the CCK8 assays, the IC50 value of cisplatin was significantly increased in HeyA8 Flag-HELQ cells compared to the control (Fig.1A). Conversely, HELQ knockdown in A2780 cells resulted in increased sensitivity to cisplatin (Fig.1B-C). To broaden our investigation, we exposed HeyA8 Flag-HELQ and control cells to a range of chemotherapeutic agents, including Etoposide, Irinotecan, Topotecan, Gemcitabine, Oxaliplatin, Paclitaxel, and Docetaxel. HELQ overexpression was found to augment resistance to these drugs, agreement with its effect on cisplatin resistance (Fig. 1D-J). Further supporting the role of HELQ in platinum resistance, *in vivo* experiments using subcutaneous xenograft tumors treated with cisplatin revealed a decrease of tumor volume in the HELQ knockdown group (Fig.1K). Flow cytometry analysis demonstrated that HELQ significantly promoted resistance to apoptosis in A2780 and HEYA8 cells induced by cisplatin, compared to the control group (Fig.S2A-B). Subsequently, an evaluation was conducted on cell cycle. HELQ abrogated cisplatin-induced G2/M cell cycle arrest in A2780 and HeyA8 cells, as demonstrated in Fig.S2C-D. Additionally, elevated HELQ expression was noted in platinum-resistant ovarian cancer tissues within the GSE51373 and GSE114206 datasets (Fig.S2A). Consistently, patients with tumors exhibiting higher HELQ expression in the TCGA dataset had a poorer prognosis (Fig.S3B). Collectively, these outcomes underscore the role of HELQ in promoting chemoresistance in OC *in vitro* and *in vivo*.

HELQ potentiates platinum-induced DNA damage repair

After finding that overexpression of HELQ led to reduced sensitivity of HeyA8 cells to DNA damage inducing drugs, we next investigated if overexpression of HELQ would affect DNA damage repair in OC cells. Immunofluorescence was employed to detect the formation of γH2AX foci in HeyA8 Flag and HeyA8 Flag-HELQ cells at various intervals following a 24-hour cisplatin treatment. As the results depicted in Fig.2A, HELQ overexpression was associated with reduced formation of γH2AX foci post-cisplatin treatment, and an accelerated decay of these foci with time (Fig. 2B). Parallel experiments conducted with A2780 shNC and A2780 shHELQ-2 cells revealed that HELQ knockdown resulted in an increased accumulation of γH2AX foci after cisplatin treatment (Fig.2C-D). Furthermore, another DNA damage markers, RPA1 and 53BP1, were determined in cells and tissues from *in vivo* OC models by western blot and IHC. Consistent with the trend of γH2AX change, RPA1 and 53BP1 subsided faster in cells with higher HELQ expression in cisplatin-treated OC models (Fig.S4A-C). These observations collectively imply that HELQ enhanced the capacity of OC cells for DNA damage repair.

The BER pathway is a potential downstream effector of HELQ-mediated chemoresistance

In an effort to elucidate the molecular mechanisms throuth which HELQ modulates sensitivity to cisplatin, we conducted comparative transcriptom analysis on HeyA8 Flag and HeyA8 Flag-HELQ cells (Fig.3A). We identified 82 up- and 170 downregulated differentially expressed genes (DEGs) using a cutoff of a fold change ≥2 and a *p*-value < 0.05. Subsequent KEGG and GO analyses on these DEGs from HeyA8 Flag-HELQ cells revealed enrichment of multiple pathways, including the p53 signaling pathway, PI3K-AKT signaling pathway, base excision repair (BER), and DNA replication and other pathways were enriched in HeyA8 Flag-HELQ cells (Fig.3B, Fig.S5A). Gene set enrichment analysis (GSEA) further indicated significant enrichment of BER, Mismatch Repair (MMR), DNA Replication, Homologous Recombination (HR), Fanconi Anemia pathway and Nucleotide Excision Repair (NER) pathways in HeyA8 Flag-HELQ cells (Fig.3C, Fig.S5B-F). These results illustrate the influence of HELQ on the modulation of DNA damage repair pathways. Considering that the relationships between HELQ and MMR or HR were previously reported [14,21,22], the BER pathway was selected for further study (Fig.3D). To clarify the specific effects of HELQ on BER pathway genes, RT-qPCR was used to detect their expression in HELQ overexpressing and downregulated cells. The expression of *MPG, LIG1, PARP1, TGD, and RPA1* was positively correlated with HELQ, among which PARP1 showedthe most significant trend (Fig.3E-F).

HELQ promotes platinum resistance by regulating PARP1 expression in OC

Taking into account the fact that the expression of *PARP1* showed the most significant change trend in HeyA8 Flag-HELQ cells as well as its key role in the BER pathway, we determined the expression of PARP1 and HELQ in OC cell lines (Fig.4A). Western blot analysis revealed a significant positive correlation between PARP1 and HELQ protein levels in these cells (Fig.4B-C). Moreover, overexpression of HELQ led to elevated PARP1 levels and *vice versa* (Fig.4D). This correlation was further validated in The Cancer Genome Atlas (TCGA) ovarian cancer dataset, where a positive association between HELQ and PARP1 was observed (Fig.4E). To establish a causal link between HELQ-mediated chemoresistance and PARP1 regulation, we utilized a PARP1-specific siRNA in HELQ-overexpressing HeyA8 cells. Efficient knockdown of PARP1 was confirmed by western blot analysis. Our results indicated that siPARP1 could reverse PARP1 upregulation induced by HELQ overexpression (Fig.4F). The CCK8 assays demonstrated that the increased cisplatin resistance conferred by HELQ overexpression was attenuated following PARP1 knockdown (Fig.4G). In addition, analysis

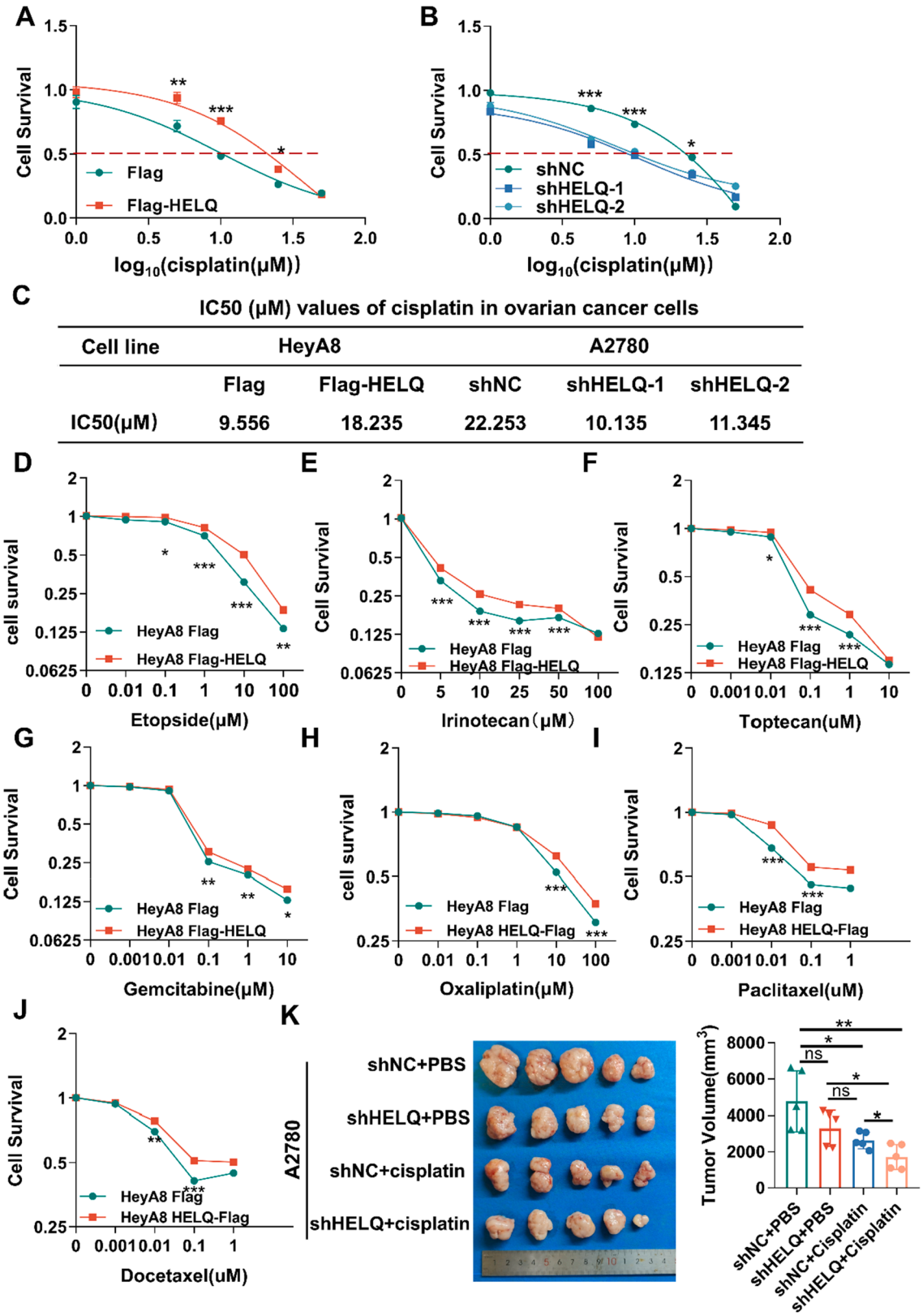


Fig. 1. HELQ promotes ovarian cancer cells chemoresistance *in vitro* and *in vivo*. A-B The cell viability curves show the results of CCK8 assays of HeyA8 Flag, HeyA8 Flag-HELQ or A2780 shNC, A2780 shHELQ-1 and A2780 shHELQ-2 cells treated with cisplatin for 48 h. **C** IC50 values of cisplatin in ovarian cancer cells based on the results of CCK8 assays. **d-J** The cell viability curves show the results of CCK8 assays of HeyA8 Flag and HeyA8 Flag-HELQ cells treated with Etoposide, Irinotecan, Topotecan, Gemcitabine, Oxaliplatin, Paclitaxel or Docetaxel for 48 h. **K** Images of subcutaneous xenografts and tumors removed from mice (left). The histograms show the tumor growth volume of each group of nude mice (right). ns, no significance, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

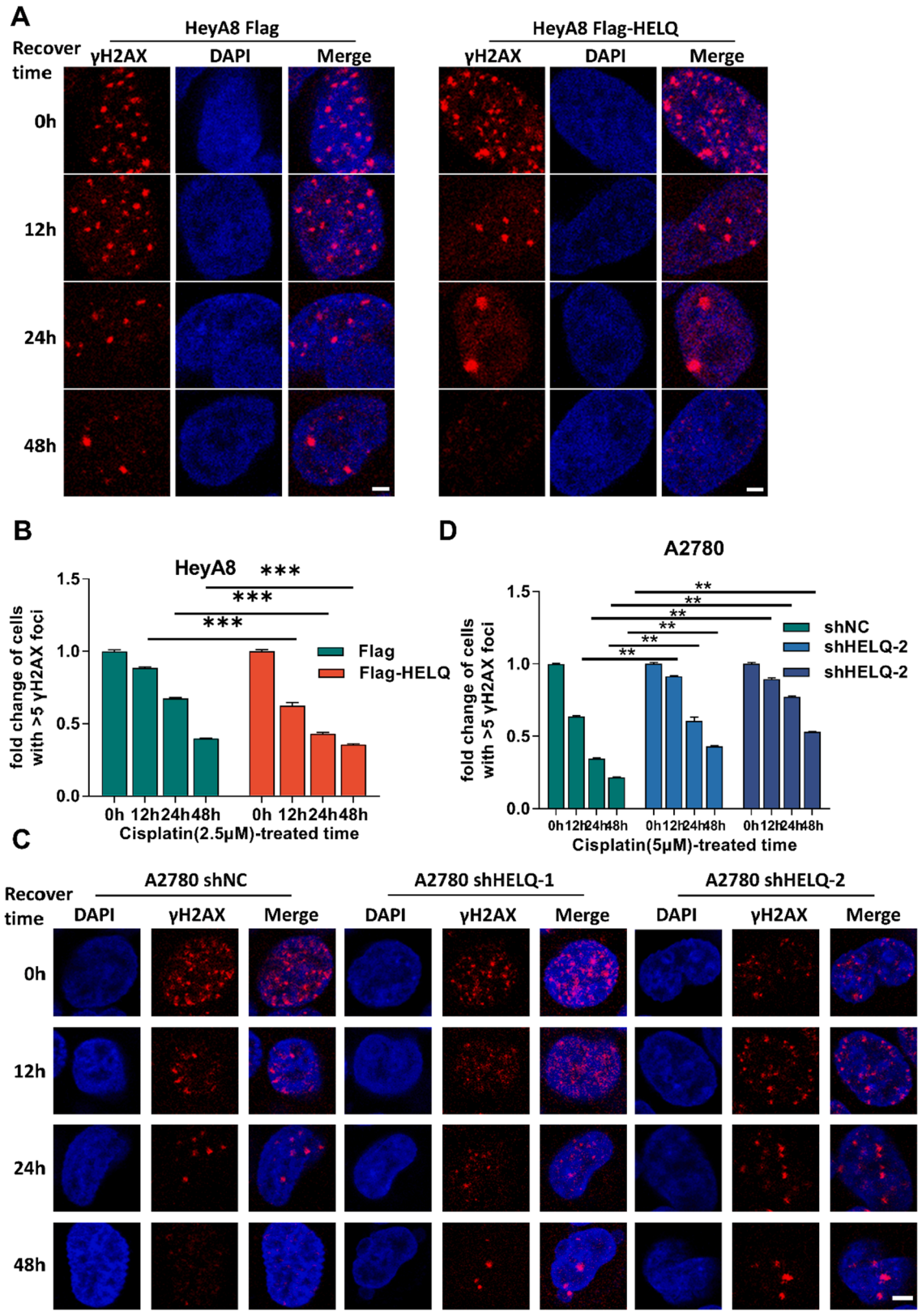


Fig. 2. HELQ promotes platinum-induced DNA damage repair. A Representative images of immunofluorescence staining show the expression of γH2AX foci (red) in HeyA8 Flag and HeyA8 Flag-HELQ cells treated with cisplatin for 0 h, 12 h, 24 h or 48 h. **B** The histograms show the relative expression γH2AX foci in HeyA8 Flag and HeyA8 Flag-HELQ cells. **C** Representative images of immunofluorescence staining show the expression of γH2AX foci (red) in A2780 shNC and A2780 shHELQ-1/2 cells treated with cisplatin for 0 h, 12 h, 24 h or 48 h. **D** The histograms show the relative expression γH2AX foci in A2780 shNC and A2780 shHELQ-1/2 cells. . Scale bar: 5 μm. ns, no significance, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

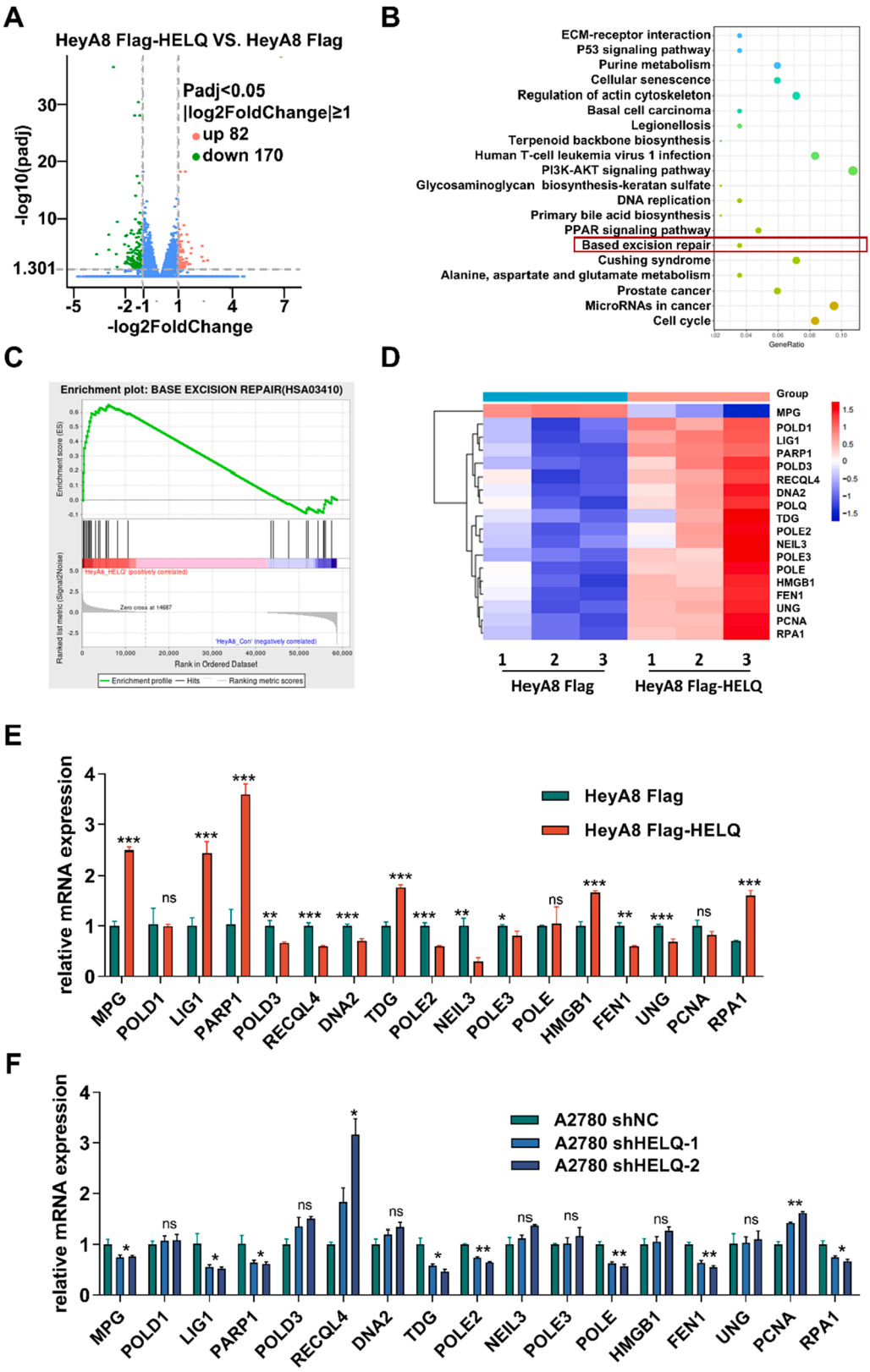


Fig. 3. BER pathway is potential HELQ downstream. A The volcano plot shows the differentially expressed genes between HeyA8 Flag and HeyA8 Flag-HELQ cells. **B** KEGG analysis of differentially expressed genes between HeyA8 Flag and HeyA8 Flag-HELQ cells. **C** GSEA enrichment analysis. The Base Excision Repair (BER) pathway is significantly enriched in the cells of high HELQ. GSEA, Gene set enrichment analysis. **D** The heatmap shows the expression of genes in BER pathway in HeyA8 Flag and HeyA8 Flag-HELQ cells. **E-F** The histograms show the mRNA expression of genes in BER pathway in HeyA8 Flag and HeyA8 Flag-HELQ cells or A2780 shNC and A2780 shHELQ-1/2 cells detected by RT-qPCR. ns, no significance, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

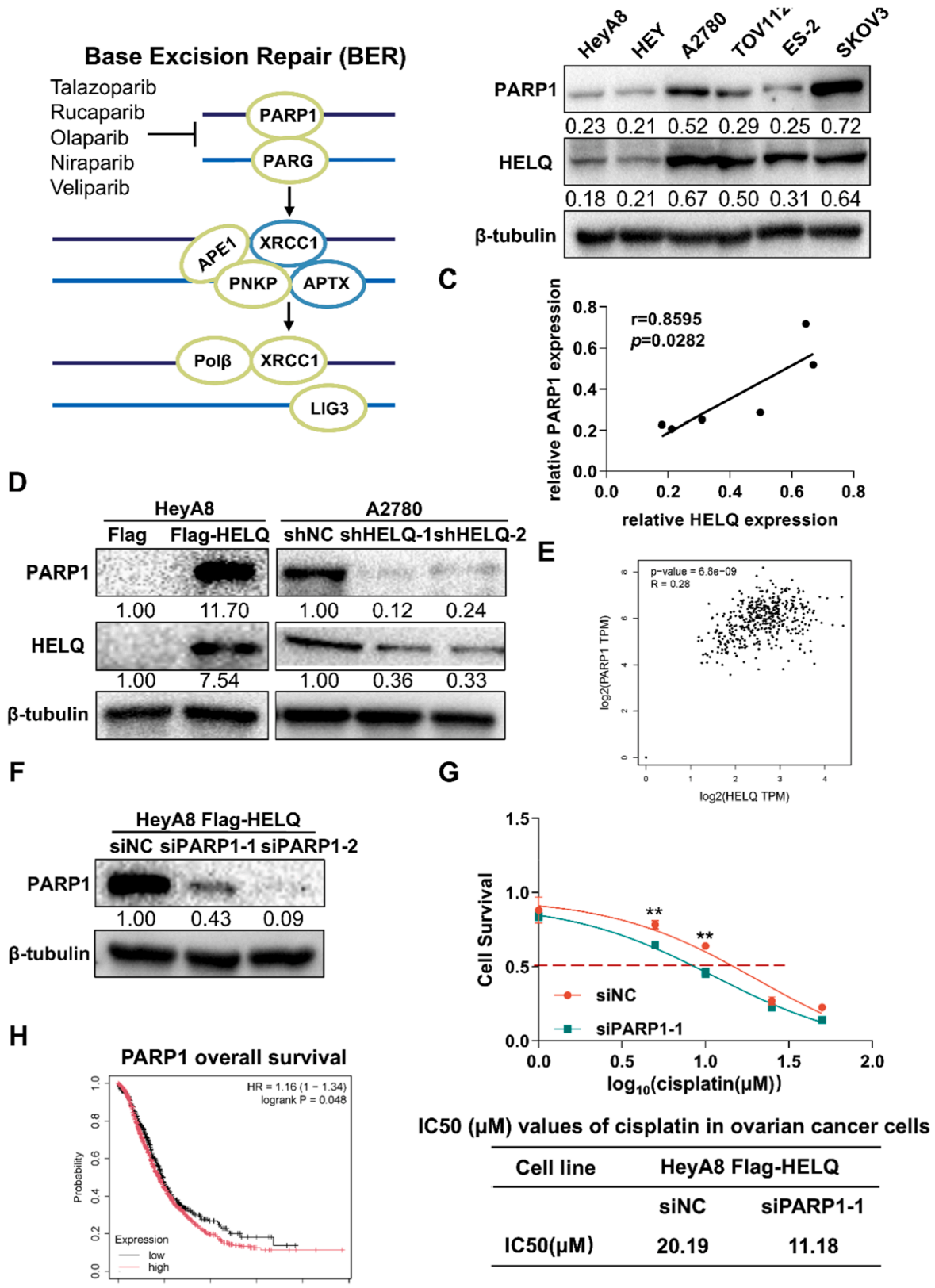


Fig. 4. HELQ promotes ovarian cancer cells platinum resistance via regulating PARP1. **A** Schematic representation of the BER pathway. **B** Western blotting images show the expression of HELQ and PARP1 in ovarian cancer cells. **C** Scatter diagrams show the correlation of HELQ and PARP1 in ovarian cancer cells. **D** Western blotting images show the expression of PARP1 in HELQ overexpressed or downregulated cells. **E** Pairwise gene correlation analysis between HELQ and PARP1 was performed by using GEPIA. **F** Western blotting images show the expression of PARP1 in HELQ overexpressed cells transfected with siRNAs for PARP1. **G** Kaplan–Meier analysis of PARP1 in ovarian cancer in ovarian cancer analysis with K–M Plotter. **H** The cell viability curves show the results of CCK8 assays of HeyA8 Flag and HeyA8 Flag-HELQ transfected with siRNAs for PARP1 and treated with cisplatin for 48 h. IC50 values of cisplatin in ovarian cancer cells based on the results of CCK8 assays. ns, no significance, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

of TCGA data indicated that higher PARP1 expression was associated with reduced overall survival in ovarian cancer patients (Fig.4H). In summary, we identified PARP1 as an essential factor for HELQ-mediated platinum resistance in ovarian cancer.

HELQ as a potential biomarker for PARPi therapy

PARP inhibitors (PARPi), primarily targeting PARP1, have become a cornerstone of maintenance therapy in ovarian cancer [23]. Given the robust correlation between PARP1 and HELQ expression in OC, we explored the potential association between HELQ expression and the therapeutic efficacy of PARP inhibitors. Initially, we assessed the IC50 values of PARPi in cells with elevated HELQ expression (Fig.5A-B). The CCK8 assays showed that upregulating HELQ remarkably enhanced the sensitivity of ovarian cancer cells to PARPi, including both Olaparib and Niraparib (Fig.5C). We next futher analyzed HELQ expression in tumor tissues from 55 OC patients who received first-line maintenance treatment with PARPi, including 32 patients treated with Olaparib and 23 with Niraparib (Fig.5D). The baseline demographic and clinical characteristics of patients are presented in Table 1, illustrating no significant disparities between low and high HELQ-expressing groups that may have influence PARPi treatment outcomes. Notebly, higher HELQ expression was observed in patients exhibiting no disease progression compared to those with progression, across both treatment groups (Fig.5E). Patients with elevated HELQ expression also demonstrated prolonged progression-free survival in the PARPi maintenance treatment cohort (Fig.5F). Although PARP1 expression was examined in the same patient cohort, no significant difference was observed between the groups (Fig.S5A-B). However, the anticipated positive correlation between HELQ and PARP1 expression was evident within this group (Fig. S5C-D). Prognostic analysis of combined expression of HELQ and PARP1 showed that patients with high HELQ and low PARP1 had a better PFS (Fig.5G).These findings collectively suggest that HELQ may serve as a promising biomarker for monitoring the response to PARPi treatment in ovarian cancer.

Discussion

DNA helicases play a pivotal role in replication, repair, and transcription by unwinding the double helix [24]. HELQ, a DNA helicase with known involvement in DNA repair and replication, has been implicated in tumor biology, particularly in the context of chemotherapy resistance [25]. Our previous work highlighted the prognostic significance of elevated HELQ expression in platinum-resistant ovarian cancer, yet the mechanistic link between HELQ and platinum resistance remained to be fully elucidated [17,18]. This study concentrated on HELQ expression in OC cell to explore and the underlying mechanisms.

Our findings indicate that HELQ promotes platinum resistance in OC by enhancing the repair of DNA damage. This is in line with prior observations that reduced HELQ levels are associated with diminished DNA repair capacity in osteosarcoma and endometrial stromal sarcoma [16,26]. We extended these findings by demonstrating that HELQ overexpression confers resistance to a spectrum of DNA damage-inducing chemotherapeutic agents beyond platinum. This suggests that tumors with high HELQ expression may exhibit reduced responses to conventional chemotherapy, warranting the exploration of alternative therapeutic strategies, such as DNA helicase inhibitors.

Through RNA sequencing, we identified a set of downstream genes potentially regulated by HELQ, several of which are known to be involved in DNA damage repair pathways, including BER, MMR, and NER. In the BER pathway, PARP1 showed the most significant expression change in OC cells, which was validated by RT-qPCR in OC cells As a consepuence, it was selected for further investigation. Our experiments confirmed that HELQ overexpression is correlated with increased PARP1 expression, while PARP1 knockdown mitigated the enhanced platinum resistance induced by HELQ. The positive correlation between HELQ and PARP1 expression in tumor tissues further supports a link between these two factors in OC pathogenesis.

PARP inhibitors have emerged as a mainstay of OC treatment, with evidence indicating their utility across all disease stages [27]. Notably, Niraparib has been approved for use as first-line maintenance therapy for advanced ovarian cancer, irrespective of BRCA mutation status [28]. Our results indicate that overexpression of HELQ can sensitize OC cells to PARPi, coupled with the observed association between high HELQ expression and better treatment outcomes, introducing HELQ as a potential biomarker for PARPi response. This is of particular interest given the limited biomarkers currently available for PARPi therapy [29]. PARP inhibitors provide a choice for patients with HELQ high expressing tumor resistant to conventional chemotherapeutics, including those with platinum-resistant disease. In the CLIO study, Olaparib offered an ORR benefit compared to chemotherapy in patients with platinum-resistant recurrent who had previously received more than four lines of treatment [30]. Recent studies have shown that PARP inhibitors impair the enzymatic activity of PARP1 [31]. The results of this recent mechanistic study on PARP inhibitors may explain our observation that PARP1 expression did not predict PARPi efficacy. The exact mechanism through which HELQ modulates PARP1 expression and activity warrants further investigation, especially considering the potential implications for therapeutic strategies for tumors with high HELQ expression, which may be resistant to conventional chemotherapy. Understanding these mechanisms may also provide insights into the role of HELQ in the response to PARP inhibitors and its potential as a novel therapeutic target in OC.

In conclusion, our study presents significant evidence that elevated HELQ expression plays a pivotal role in the chemoresistance typical of ovarian cancer, which is likely mediated by the upregulation of PARP1 expression. The potential of HELQ as an innovative biomarker for monitoring the clinical responses to both chemotherapy and PARP inhibitor treatment is a noteworthy advancement (Fig.6). Our findings illustrate the molecular underpinnings of chemoresistance in ovarian cancer and offer a promising therapeutic target, as well as a prognostic indicator for the efficacy of PARP inhibitor therapies. Thismay lead to more personalized and effective treatment strategies for patients with ovarian cancer, particularly those facing challenges of chemoresistance.

Abbreviations

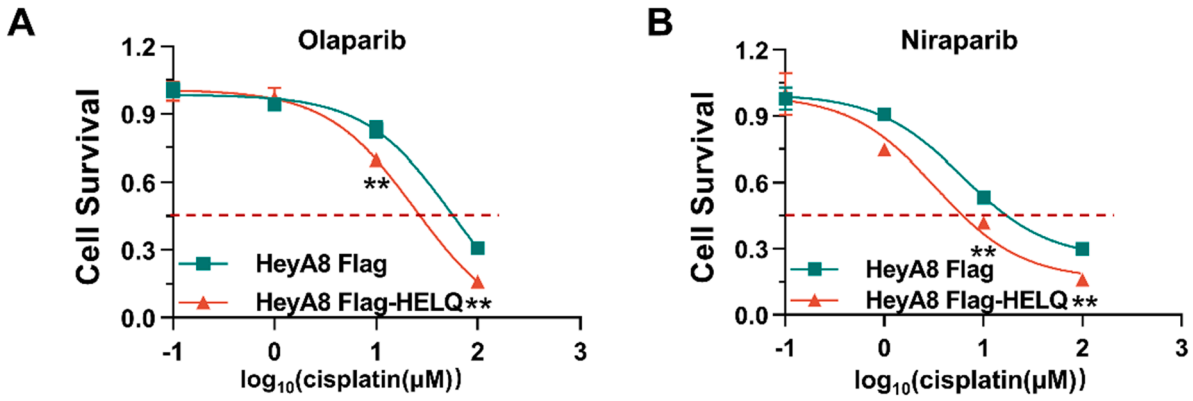
OC: ovarian cancer
HELQ: POLQ-like helicase
PARP1: poly (ADP-ribose) polymerase 1
PARPi: poly (ADP-ribose) polymerase inhibitor
BER: Base Excision Repair
NER: Nucleotide Excision Repair
MMR: Mismatch Repair
HRR: Homologous Recombination Repair
RT-qPCR: Real-time Quantitative Reverse Transcription Polymerase Chain Reaction
WB: Western blotting
IHC: Immunohistochemistry
PFS: Progression-free survival

Supplemental information

Document S1. Figures S1–S6 and Table S1-S3.

Data statement

The data are available from the corresponding author on reasonable request.



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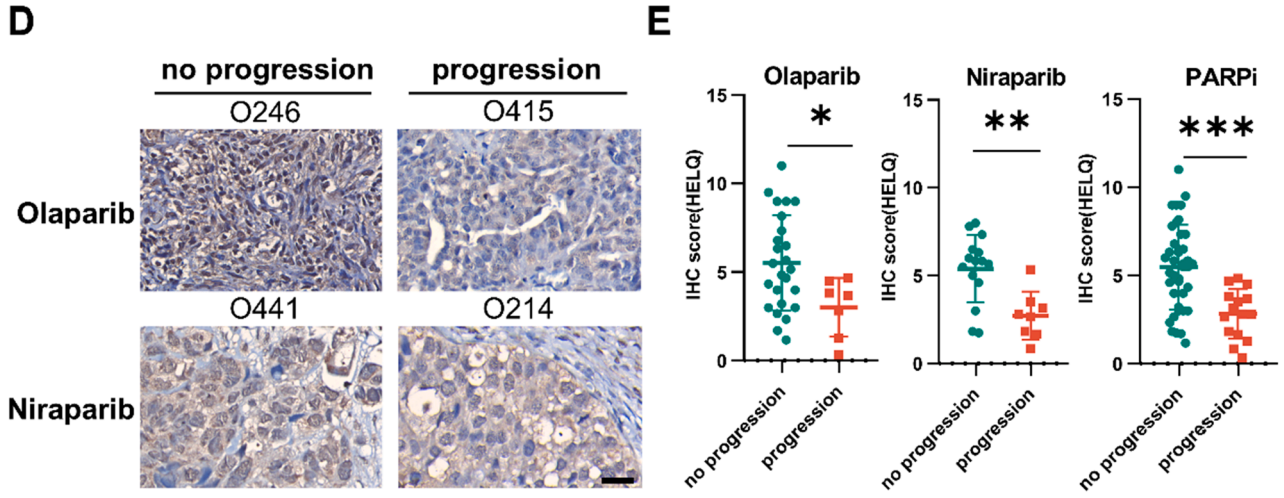
IC50 (μM) values of PARPi in ovarian cancer cells

PARPi	Olaparib		Niraparib	
HeyA8	Flag	Flag-HELQ	Flag	Flag-HELQ
IC50(μM)	57.09	24.18	6.145	4.796



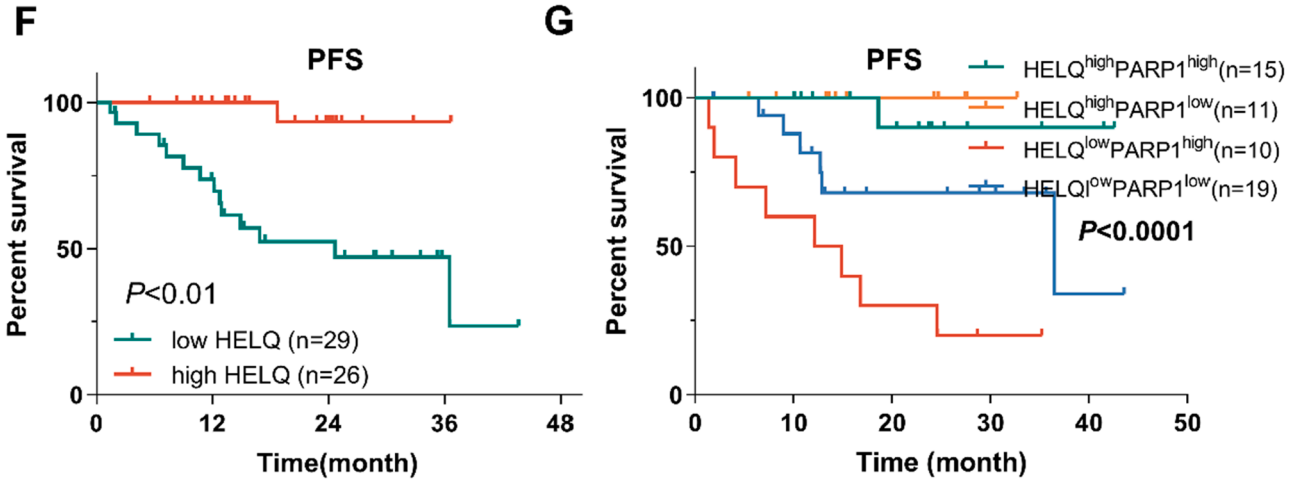


Fig. 5. HELQ is associated with first-line PARPi maintenance treatment response in ovarian cancer. A-B The cell viability curves show the results of CCK8 assays of HeyA8 Flag, HeyA8 Flag-HELQ cells treated with Olaparib or Niraparib for 48 h. **C** IC50 values of Olaparib or Niraparib in ovarian cancer cells based on the results of CCK8 assays. **D** Representative images of immunohistochemical staining of HELQ in tumor tissues from ovarian cancer patients who received PARPi for fist-line maintenance treatment. **E** The diagrams show the expression of HELQ in ovarian cancer based on IHC assays. **F** Kaplan–Meier survival curves of progression-free survival (PFS) in 55 OC patients based on HELQ IHC stains (log–rank test). **G** Kaplan–Meier survival curves of progression-free survival (PFS) in 55 OC patients based on HELQ and PARP1 IHC stains (log–rank test). Scale bar: 20 μm. ns, no significance, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

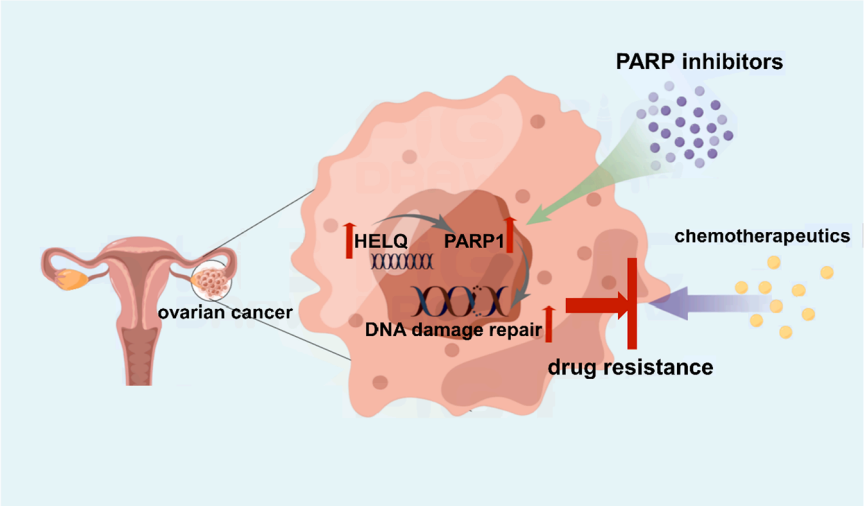


Fig. 6. A schematic diagram of proposed mechanism. HELQ, by upregulating PARP1, fosters platinum resistance in OC and warrants consideration as an emerging biomarker for monitoring therapeutic responses to chemotherapy and a predictor for PARP inhibitor treatment in ovarian cancer.

CRediT authorship contribution statement

Shuran Tan: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Fang Zhu:** Writing – original draft, Visualization, Software, Methodology, Funding acquisition. **Yi Li:** Validation, Supervision, Formal analysis. **Xinxin Wen:** Software, Investigation, Formal analysis. **Siyu Yang:** Investigation. **Zexi Liao:** Investigation. **Xuerui Duan:** Investigation. **Di Xiao:** Supervision, Resources, Project administration. **Yu Zhang:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (3) (2021) 209–249.
[2] L. Kuroki, S.R. Guntupalli, Treatment of epithelial ovarian cancer, BMJ 371 (2020) m3773.
[3] P.M. Webb, S.J. Jordan, Global epidemiology of epithelial ovarian cancer, Nat. Rev. Clin. Oncol. 21 (5) (2024) 389–400.
[4] J. St Laurent, J.F Liu, Treatment approaches for platinum-resistant ovarian cancer, J. Clin. Oncol. 42 (2) (2024) 127–133.
[5] I. Ray-Coquard, P. Pautier, S. Pignata, D. Pérol, A. González-Martín, R. Berger, et al., Olaparib plus Bevacizumab as first-line maintenance in ovarian cancer, N. Engl. J. Med. 381 (25) (2019) 2416–2428.
[6] S.L. Cooke, J.D. Brenton, Evolution of platinum resistance in high-grade serous ovarian cancer, Lancet Oncol. 12 (12) (2011) 1169–1174.
[7] K. El Bairi, S. Singh, C. Le Page, Revisiting platinum-resistant ovarian cancer: advances in therapy, molecular biomarkers, and clinical outcomes, Semin. Cancer Biol. 77 (2021) 1–2.
[8] D.T. Stefanou, V.L. Souliotis, R. Zakopoulou, M. Liontos, A. Bamias, DNA damage repair: predictor of platinum efficacy in ovarian cancer? Biomedicines. 10 (1) (2021).
[9] M.A. Khan, K.S. Vikramdeo, S.K. Sudan, S. Singh, A. Wilhite, S. Dasgupta, et al., Platinum-resistant ovarian cancer: from drug resistance mechanisms to liquid biopsy-based biomarkers for disease management, Semin. Cancer Biol. 77 (2021) 99–109.
[10] H. Tang, S. Kulkarni, C. Peters, J. Eddison, M. Al-Ani, S. Madhusudan, The current status of DNA-repair-directed precision oncology strategies in epithelial ovarian cancers, Int. J. Mol. Sci. 24 (8) (2023).
[11] I.L. Woodman, K. Brammer, E.L. Bolt, Physical interaction between archaeal DNA repair helicase Hel308 and replication protein A (RPA), DNa Repair. (Amst) 10 (3) (2011) 306–313.
[12] L. Stolk, J.R. Perry, D.I. Chasman, C. He, M. Mangino, P. Sulem, et al., Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways, Nat. Genet. 44 (3) (2012) 260–268.
[13] K. Takata, S. Reh, J. Tomida, M.D. Person, R.D. Wood, Human DNA helicase HELQ participates in DNA interstrand crosslink tolerance with ATR and RAD51 paralogs, Nat. Commun. 4 (2013) 2338.
[14] C.A. Adelman, R.L. Lolo, N.J. Birkbak, O. Murina, K. Matsuzaki, Z. Horejsi, et al., HELQ promotes RAD51 paralogue-dependent repair to avert germ cell loss and tumorigenesis, Nature 502 (7471) (2013) 381–384.
[15] S.W. Luebben, T. Kawabata, M.K. Akre, W.L. Lee, C.S. Johnson, M.G. O'Sullivan, et al., Helq acts in parallel to Fancc to suppress replication-associated genome instability, Nucleic. Acids. Res. 41 (22) (2013) 10283–10297.
[16] D.N. Liu, Y.F. Zhou, A.F. Peng, X.H. Long, X.Y. Chen, Z.L. Liu, et al., HELQ reverses the malignant phenotype of osteosarcoma cells via CHK1-RAD51 signaling pathway, Oncol. Rep. 37 (2) (2017) 1107–1113.
[17] J. Long, J.Y. Zhu, Y.B. Liu, K. Fu, Y. Tian, P.Y. Li, et al., Helicase POLQ-like (HELQ) as a novel indicator of platinum-based chemoresistance for epithelial ovarian cancer, Gynecol. Oncol. 149 (2) (2018) 341–349.
[18] F. Zhu, S. Yang, M. Lei, Q. He, L. Wu, Y. Zhang, DNA repair protein HELQ and XAB2 as chemoresponse and prognosis biomarkers in ascites tumor cells of high-grade serous ovarian cancer, J. Oncol. 2022 (2022) 7521934.
[19] S. Tan, Y. Chen, S. Du, W. Li, P. Liu, J. Zhao, et al., TIE2-high cervical cancer cells promote tumor angiogenesis by upregulating TIE2 and VEGFR2 in endothelial cells, Transl. Oncol. 26 (2022) 101539.
[20] Z. Tang, C. Li, B. Kang, G. Gao, C. Li, Z. Zhang, GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses, Nucleic. Acids. Res. 45 (W1) (2017) W98–w102.
[21] Y. Zhao, K. Hou, Y. Li, S. Hao, Y. Liu, Y. Na, et al., Human HELQ regulates DNA end resection at DNA double-strand breaks and stalled replication forks, Nucleic. Acids. Res. 51 (22) (2023) 12207–12223.
[22] J.A. Kamp, B. Lemmens, R.J. Romeijn, S.C. Changoer, R. van Schendel, M. Tijsterman, Helicase Q promotes homology-driven DNA double-strand break repair and prevents tandem duplications, Nat. Commun. 12 (1) (2021) 7126.
[23] D.L. Richardson, R.N. Eskander, D.M O'Malley, Advances in ovarian cancer care and unmet treatment needs for patients with platinum resistance: a narrative review, JAMa Oncol. 9 (6) (2023) 851–859.
[24] R.M. Brosh, Jr. DNA helicases involved in DNA repair and their roles in cancer, Nat. Rev. Cancer 13 (8) (2013) 542–558.
[25] N. Tang, W. Wen, Z. Liu, X. Xiong, Y. Wu, HELQ as a DNA helicase: its novel role in normal cell function and tumorigenesis (Review), Oncol. Rep. 50 (6) (2023).
[26] Y. Liu, Y. Zhang, Y. Tian, [Expressions of HELQ and RAD51C in endometrial stromal sarcoma and their clinical significance], Nan. Fang. Yi. Ke Da Xue Xue Bao 40 (7) (2020) 936–941.

[27] H. Li, Z.Y. Liu, N. Wu, Y.C. Chen, Q. Cheng, J. Wang, PARP inhibitor resistance: the underlying mechanisms and clinical implications, Mol. Cancer 19 (1) (2020) 107.
[28] Lee A. Niraparib, A review in first-line maintenance therapy in advanced ovarian cancer, Target. Oncol. 16 (6) (2021) 839–845.
[29] J. Mateo, C.J. Lord, V. Serra, A. Tutt, J. Balmaña, M. Castroviejo-Bermejo, et al., A decade of clinical development of PARP inhibitors in perspective, Ann. Oncol. 30 (9) (2019) 1437–1447.
[30] A. Vanderstichele, L. Loverix, P. Busschaert, E. Van Nieuwenhuysen, S.N. Han, N. Concin, et al., Randomized CLIO/BGOG-ov10 trial of olaparib monotherapy *versus* physician's choice chemotherapy in relapsed ovarian cancer, Gynecol. Oncol. 165 (1) (2022) 14–22.
[31] M. Petropoulos, A. Karamichali, G.G. Rossetti, A. Freudenmann, L.G. Iacovino, V. S. Dionellis, et al., Transcription-replication conflicts underlie sensitivity to PARP inhibitors, Nature 628 (8007) (2024) 433–441.