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Review Article

Unraveling role of ubiquitination in drug resistance of gynecological cancer

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Abstract: Chemotherapy is the principal treatment for advanced cancer patients. However, chemotherapeutic resistance, an important hallmark of cancer, is considered as a key impediment to effective therapy in cancer patients. Multiple signaling pathways and factors have been underscored to participate in governing drug resistance. Post-translational modifications, including ubiquitination, glycosylation, acetylation and phosphorylation, have emerged as key players in modulating drug resistance in gynecological tumors, such as ovarian cancer, cervical cancer and endometrial cancer. In this review article, we summarize the role of ubiquitination in governing drug sensitivity in gynecological cancers. Moreover, we describe the numerous compounds that target ubiquitination in gynecological cancers to reverse chemotherapeutic resistance. In addition, we provide the future perspectives to fully elucidate the mechanisms by which ubiquitination controls drug resistance in gynecological tumors, contributing to restoring drug sensitivity. This review highlights the complex interplay between ubiquitination and drug resistance in gynecological tumors, providing novel insights into potential therapeutic targets and personalized treatment strategies to overcome the bottleneck of drug resistance.

Keywords: PTM, ubiquitination, gynecological cancer, drug resistance, treatment, target

Introduction

Gynecological tumors, mainly comprising ovarian, cervical, and endometrial cancers, represent a substantial health burden worldwide, impacting female health across various age groups [1, 2]. Despite significant advancements in early detection and therapeutic strategies, these malignancies remain formidable to manage due to the emergence of drug resistance, which often leads to treatment failure and malignant disease progression [3, 4]. Over the past few decades, extensive research efforts have been dedicated to unraveling the intricate interplay between translational research and the complex mechanisms of drug resistance, with the aim of shedding light on the underlying complexities of gynecological tumors [5, 6]. Of particular concern is the formidable challenge posed by the emergence of drug resistance mechanisms, which significantly hinders the effective treatment of gynecological tumors [7]. Ovarian cancer, which is frequently diagnosed at advanced stages, exhibits a pronounced propensity for developing resistance to platinum-based chemotherapies, which are considered the cornerstone of first-line treatment [8, 9]. Similarly, cervical cancer, primarily associated with persistent human papillomavirus (HPV) infection, can manifest resistance to both radiotherapy and platinum agents, further complicating therapeutic interventions [10, 11]. Additionally, endometrial cancer, a prevalent malignancy of the female reproductive system, also encounters obstacles related to drug resistance, impacting the efficacy of hormonal therapies and other targeted interventions [12].

In recent years, posttranslational modifications (PTMs) have emerged as key regulators of cel-

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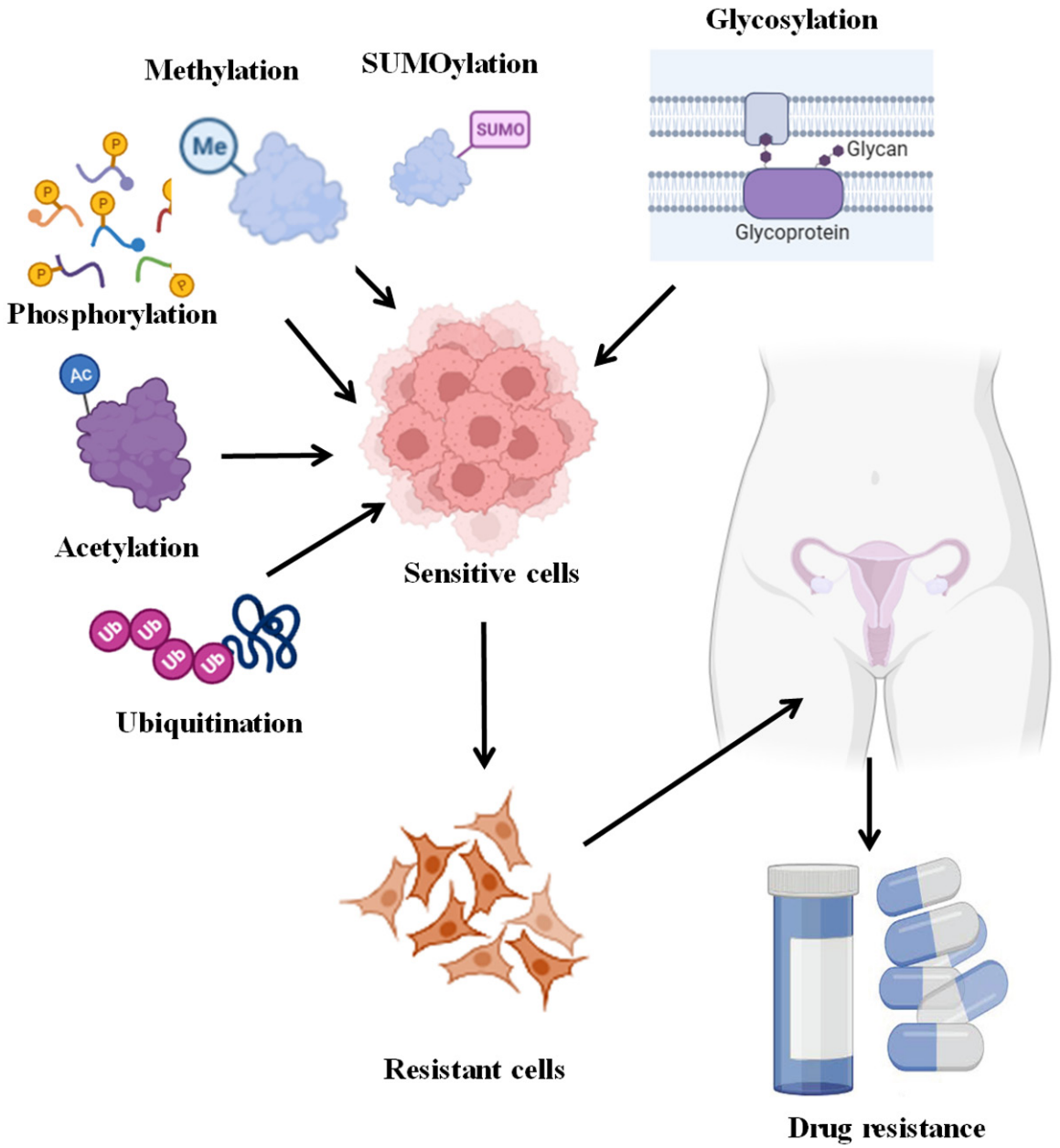

Figure 1. PTMs participate in drug resistance of gynecological cancers. These PTMs include ubiquitination, acetylation, glycosylation, phosphorylation, methylation and SUMOylation.

lular processes, influencing various aspects of protein function, stability, and cellular signaling [13-15]. Among these modifications, phosphorylation, acetylation, ubiquitination, O-GlcNAcylation and SUMOylation have been extensively studied for their roles in cancer biology [16-20]. Dysregulation of these modifications can lead to altered cellular responses, ultimately contributing to the development of drug resistance in cancer cells [21-24]. In the context of gynecological tumors, compelling evidence suggests that specific PTMs of key regulatory proteins are associated with drug resistance phenotypes (**Figure 1**). This comprehensive review aimed to explore the intricate link between ubiquitination and drug resistance in gynecological tumors. By consolidating current research findings and the latest advancements in our understanding of ubiquitination, we endeavored to provide a comprehensive

and insightful perspective on the impact of ubiquitination on drug resistance in ovarian, cervical, and endometrial cancers. Furthermore, we shed light on potential therapeutic strategies targeting ubiquitination, with the goal of enhancing drug sensitivity and improving the clinical management of gynecological malignancies. Through this comprehensive exploration, we aspired to contribute significantly to the advancement of precision medicine approaches and the development of personalized therapeutic strategies for patients facing drug-resistant gynecological tumors, ultimately improving patient outcomes and quality of life.

Ubiquitination and deubiquitination in gynecological cancer

Ubiquitination is an enzymatic cascade that is conducted by the E1 Ub-activating enzyme, the E2 Ub-conjugating enzyme, and the E3 Ub-protein ligase, leading to the transfer of ubiquitin, a 76 amino-acid protein, to the target proteins [25, 26]. E3 ubiquitin ligases are responsible for selecting specific substrates for ubiquitination and degradation [27]. There are three classes of E3 ligases: RING-type, homologous to the E6-AP carboxyl terminus (HECT)-type, and RBR-type [28, 29]. Ring-type E3 ligases are characterized by the presence of a ring-finger domain, a specialized zinc-finger structure that is crucial for their function. This domain enables the enzyme to interact with both the E2 enzyme and the substrate protein, thus catalyzing the ubiquitin transfer [30, 31]. RING-type E3 ligases include the Skp1-Cullin-F-box (SCF) complex and the Anaphase Promoting Complex/Cyclosome (APC/C). The SCF complex is a multi-protein E3 ubiquitin ligase complex that is composed of four main components [32, 33]. S-phase kinase-associated protein 1 (Skp1) acts as an adaptor. Cullin serves as a scaffold for the complex. The F-box protein determines substrate specificity [34]. Different F-box proteins target a wide range of substrates [35]. RING-finger proteins (such as Rbx1/Roc1) mediate the transfer of ubiquitin from the E2 enzyme to the substrate. The APC/C, a highly complex E3 ubiquitin ligase, mainly regulates the cell cycle, primarily by driving cell cycle transitions from metaphase to anaphase and from anaphase to G1 [36]. The APC/C consists of several core subunits and is regulated by coactivators such as Cdc20 and Cdh1 [37, 38], which maintain substrate specificity [39, 40].

HECT-type E3 ligases are a distinct group of enzymes involved in the ubiquitination process and have unique HECT domains. This domain is structurally different from that of RING-type E3 ligases [41, 42]. In the ubiquitination process, the HECT domain directly participates in the transfer of ubiquitin to the target protein [43]. Unlike RING-type E3 ligases, HECT-type E3 ligases form a transient thioester bond with ubiquitin before transferring it to the substrate protein [44]. The neural precursor cell expressed, developmentally down-regulated 4 (NEDD4) family is a good example of HECT-type E3 ligases [45]. The NEDD4 family is characterized by several structural features: a HECT domain, WW domains, and a C2 domain. The HECT domain is involved in the direct transfer of ubiquitin to the substrate proteins. WW domains mediate protein-protein interactions. These domains recognize proline-rich peptide motifs in target proteins or in regulatory proteins. The C2 domain can bind to phospholipids and is involved in the localization of the ligase to cellular membranes [46, 47]. The nine members of the NEDD4 family are NEDD4-1 (also known as NEDD4), NEDD4-2 (also known as NEDD4L), ITCH, WWP1, WWP2, SMURF1, SMURF2, NEDL1 (HECW1) and NEDL2 (HECW2) [48-50].

Deubiquitination is conducted by deubiquitinases (DUBs), which can remove the ubiquitin from proteins involved in the regulation of diverse cell processes, including the cell cycle, apoptosis, autophagy, proliferation and differentiation [51, 52]. DUBs, a group of enzymes, play a crucial role in the process of removing ubiquitin molecules from targeted proteins. DUBs are involved in ensuring a balance in the ubiquitination-deubiquitination cycle to maintain cellular homeostasis [53, 54]. These enzymes counteract the action of ubiquitin ligases, and thus, DUBs can rescue proteins from being targeted for degradation. There are several classes of DUBs, including the ubiquitin-specific proteases (USP) and OTU domain-containing proteases (OTUD) families, each characterized by distinct structural motifs and substrate specificities [55, 56]. Ubiquitination plays an essential role in the regulation of drug resistance in gynecological cancer [57].

Ovarian cancer

Ubiquitination and deubiquitination mediate chemotherapy sensitivity in ovarian cancer [58,

59]. One group used the 2-DE approach and the ESI-Q-TOF MS/MS method and detected differential protein expression profiles between cisplatin-resistant and cisplatin-sensitive ovarian cancer cells. Ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1) was identified as a key regulatory factor in the modulation of cisplatin resistance in ovarian cancer [60]. Another group showed that p62 enhanced the mitochondrial localization of p53 via interaction with its UBA domain, leading to the modulation of cisplatin sensitivity in ovarian cancer cells, indicating the critical role of the UPS in cisplatin resistance in ovarian cancer cells [61]. AEBP2, a zinc finger protein, is crucial for controlling the growth and response to cisplatin, a widely used chemotherapy drug, in ovarian cancer cells [62, 63]. The genetic elimination of AEBP2 impedes ovarian cancer cell proliferation and enhances ovarian cancer cell sensitivity to cisplatin. However, AEBP2 itself is subject to ubiquitination, which is marked for degradation by the SCF β-TrCP ubiquitin ligase complex. Failure of its effective degradation leads to the development of cisplatin resistance in ovarian cancer [62]. Similarly, Fn14 overexpression has been shown to suppress cisplatin resistance in OVCAR-3 ovarian cancer cells. This occurs through a reduction in Hsp90 expression and disruption of the Mdm2-p53-R248Q-Hsp90 complex, which is achieved by the Mdm2-mediated ubiquitin-proteasome pathway [64].

UBC13, a critical player, is capable of reversing paclitaxel resistance in ovarian cancer. Downregulating UBC13 expression attenuates UBC13 ubiquitination and elevates DNMT1 levels, leading to enhanced DNA methylation on the CHFR promoter. As a result, CHFR expression is reduced, and Aurora A levels are increased, effectively countering paclitaxel resistance [65]. Furthermore, SIAH1, which acts as a ubiquitin ligase, employs its RING domain to promote the ubiquitination and subsequent degradation of RPS3. Dysregulation of RPS3 expression or loss of SIAH1-mediated ubiquitination through the K214R mutant significantly impairs platinum-induced tumor suppression. This highlights the critical role of the SIAH1-RPS3-NF-κB axis in addressing therapeutic resistance in epithelial ovarian cancer [66]. Additionally, the upregulation of Parkin expression has shown promise in inhibiting the proliferation of chemotherapy-resistant ovarian cancer cells by promoting the ubiquitination and degradation of p53 [67]. OGT modulates the ubiquitination and degradation of NRF2 in ovarian cancer cells by modifying KEAP1 through glycosylation, thus influencing ovarian cancer cell resistance to cisplatin [68].

Another vital study showed that in ovarian cancer cells, RING1A mediates the monoubiquitination of phosphorylated H2AX (γH2AXub1) at lysine 119 sites during platinum-induced DNA damage. Consequently, RING1A deficiency impairs the activation of the G2-M DNA damage checkpoint, reducing the ability of ovarian cancer cells to repair platinum-induced DNA damage and increasing their sensitivity to platinum agents [69]. Ubiquitin-specific protease 14 (USP14) is a biomarker for the occurrence of cisplatin resistance in ovarian cancer. The expression of USP14 is downregulated in cisplatin-resistant A2780 cells. Suppression of USP14 counteracts cisplatin cytotoxicity via enhancement of connexin 32 (Cx32) internalization in ovarian cancer cells [70]. Another study showed that USP14 confers cisplatin resistance by targeting the BCL6 oncoprotein to prevent its proteasomal-dependent degradation in ovarian cancer [71]. Reduced expression of USP15 is observed in ovarian tumor tissues with paclitaxel resistance [72]. USP8 activity is elevated in cisplatin-resistant ovarian cancer cells. Depletion of USP8 enhances cisplatin sensitivity and inactivates receptor tyrosine kinases in ovarian cancer cells. USP8 downregulation promotes cisplatin-mediated caspase 3/7 activation and survivin downregulation in ovarian cancer cells, leading to the promotion of cell apoptosis [73].

Akt contributes to resistance, partially by regulating the ubiquitination of FLIP, which is induced by cisplatin and dependent on p53 [74]. Notably, acquired cisplatin-resistant ovarian cancer cells exhibit elevated levels of MKP-1 and PARP-1 protein expression, and silencing either protein improves the sensitivity of resistant cells to cisplatin [75]. Additionally, the direct binding of CENPK to SOX6 results in changes to its interaction with β-catenin, leading to increased expression and translocation of β-catenin into the nucleus. This, in turn, promotes the ubiquitination of p53, activating the Wnt/β-catenin signaling pathway while suppressing the p53 pathway. As a consequence

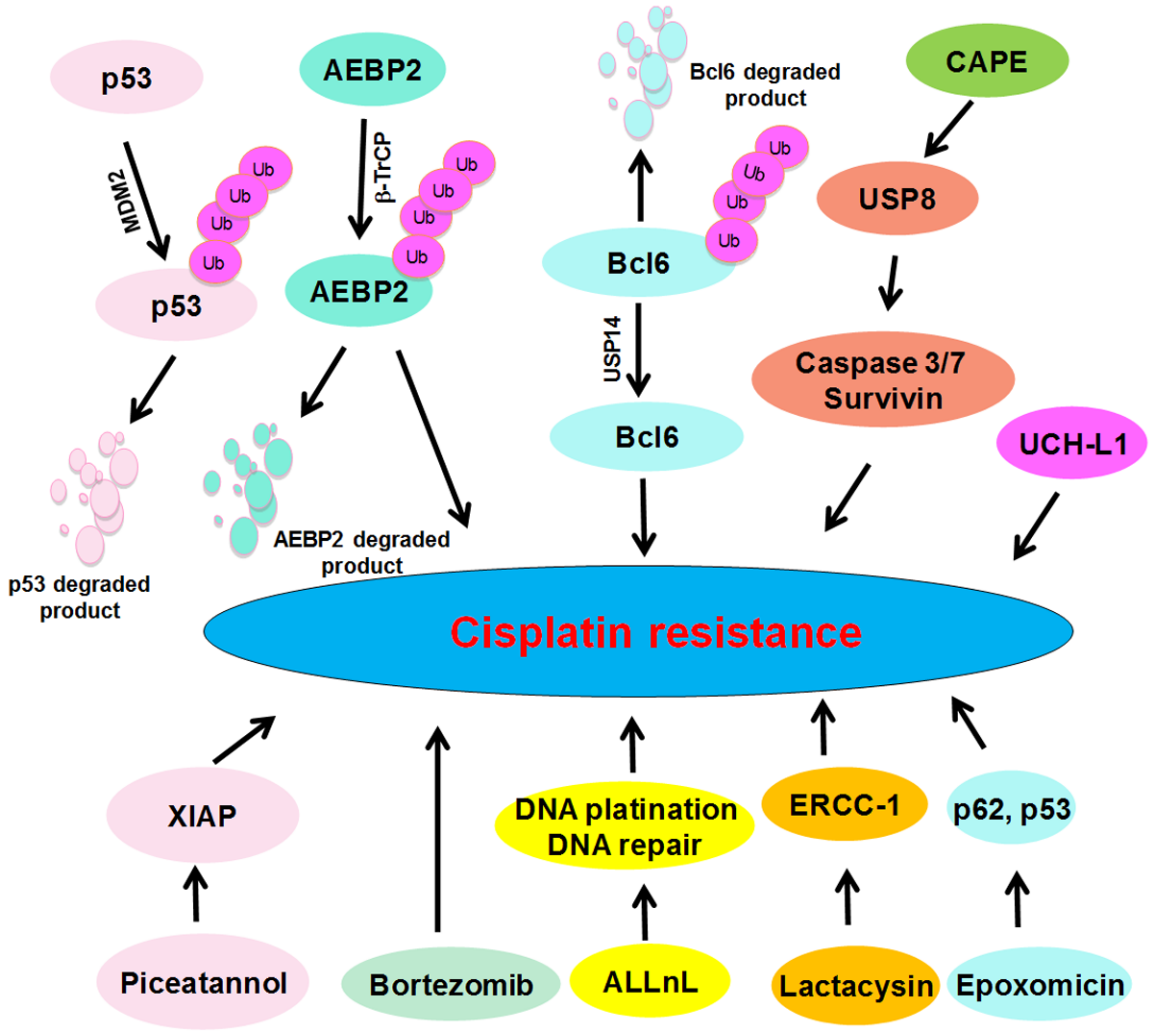

Figure 2. Ubiquitination plays a critical role in cisplatin resistance in ovarian cancer cells. Multiple compounds target ubiquitination to overcome the drug resistance of ovarian cancer cells.

of this dysregulation, epithelial-mesenchymal transition (EMT), which is involved in metastasis; DNA replication, which promotes tumor cell proliferation; and tumorigenic pathways, which are crucial for cell stemness, are ultimately enhanced [76]. Higher expression of CRL4 is observed in cisplatin-resistant ovarian cancer cells. Downregulation of CRL4 by shRNA infection reverses cisplatin resistance via inhibition of BIRC3 by mediating STAT3 in ovarian cancer cells [77]. These compelling discoveries underscore the pivotal role of ubiquitination in modulating drug resistance mechanisms in ovarian tumors, providing potential avenues for developing targeted therapies to overcome resistance and improve treatment outcomes (**Figure 2**).

Cervical cancer

USP15 downregulation leads to paclitaxel resistance in HeLa cells by impairing the stability and activity of caspase-3. Decreased expression of USP15 is observed in paclitaxel-resistant ovarian cancer tissues, suggesting that USP15 could be a diagnostic biomarker for paclitaxel-resistant cancer [72]. One study revealed that miR-100 expression is high in HeLa and SiHa cells under hypoxic conditions. USP15 was identified as a target of miR-100, and hypoxia inhibited the expression of USP15. Upregulation of miR-100 leads to paclitaxel resistance in cervical cancer cells by targeting USP15 [78]. The SPOP E3 ligase has been confirmed to play an essential role in tumorigene-

sis and cancer treatment [79]. Wu et al. reported that SPOP expression is elevated in cervical cancer patients with pelvic lymph node metastasis and is correlated with poor prognosis. SPOP enhances the proliferation and metastasis of cervical cancer cells. SPOP triggers the spatial separation of PD-1 from PD-L1 in spatial localization and achieves immune tolerance, contributing to cervical cancer progression [80]. DRAK1 expression is downregulated in paclitaxel-resistant cervical cancer cells, which is accompanied by the upregulation of TRAF6 expression and NF-κB activation. Downregulation of DRAK1 increases paclitaxel resistance in cervical cancer cells, while overexpression of DRAK1 represses cell growth in paclitaxel-resistant cervical cancer cells. Chemoresistant cervical cancer samples exhibit lower expression of DRAK1. SPOP targets DRAK1 for ubiquitination and degradation and induces the growth of paclitaxel-resistant cervical cancer cells [81].

CUL4A expression is elevated in patients with cervical squamous cell carcinoma and is associated with tumor stage, lymph node metastasis and poor prognosis. Downregulation of CUL4A curtails cell proliferation, invasion and migration in cervical cancer. Silencing of CUL4A enhances cisplatin sensitivity in cervical cancer cells [82]. USP45 is illustrated to bind to Myc and cause its deubiquitination and stabilization. Overexpression of USP45 increases the expression of MYC and promotes cancer stemness and drug resistance. Knockdown of MYC abolishes USP45-mediated drug resistance and stemness [83]. The compound α-mangostin can inhibit the expression of USP45 and abrogate cancer stemness and drug resistance. Specifically, α-mangostin in combination with doxorubicin alleviates USP45-triggered cervical oncogenesis [83]. Centromere protein K (CENPK) is highly expressed in cervical tissues and is correlated with poor prognosis and cancer recurrence. Knockdown of CENPK prolongs survival time and improves chemotherapeutic effects in cervical cancer-bearing mice. Mechanistically, CENPK interacts with SOX6 and impairs the binding between CENPK and β-catenin, leading to the promotion of β-catenin expression and nuclear translocation, the upregulation of p53 ubiquitination, the inactivation of the p53 signaling pathway and the activation of the Wnt/β-catenin pathway, which ultimately promotes cancer cell stemness, EMT and cisplatin/carboplatin resistance in cervical cancer [84].

HAUSP reportedly stabilizes Cdc25A protein level in cervical cancer cells. Silencing of HAUSP reduces Cdc25A-involved colony formation and migration in HeLa cells. Furthermore, HAUSP knockdown alleviates tumor progression in mice. HAUSP increases resistance to DNA-damaging agents due to stabilization of the Cdc25A protein [85]. iASPP, an EMT inducer, stimulates cisplatin resistance in cervical cancer cells. Downregulation of iASPP reduces cell proliferation and sensitizes cervical cancer cells to cisplatin. iASPP increases the expression of miR-20a and subsequently induces EMT and cisplatin chemoresistance. Furthermore, miR-20a suppresses the expression of FBXL15 and BTG3 in cervical cancer cells. Lower expression of FBXL5 and BTG3 is observed in cervical cancer tissues and is linked to poor outcomes in cervical cancer patients [86]. One study revealed that the copper chelator D-penicillamine in combination with oxaliplatin suppresses tumor growth in oxaliplatin-resistant SiHa cervical cancer cells. D-penicillamine increases the expression of the hCtr1 protein, a copper influx transporter, via the promotion of Sp1 expression, leading to p53 translocation to the cytosol from the nucleus and the induction of p53 ubiquitination and degradation as well as the suppression of the copper efflux transporter ATP7A [87]. Downregulation of CITED2 by shRNA results in cisplatin sensitivity via the promotion of p53 stabilization [88].

Endometrial cancer

Several studies have shown the critical role of ubiquitination in the regulation of drug resistance in endometrial cancer. For example, RNF8 expression at the mRNA and protein levels is elevated in doxorubicin- and cisplatin-resistant endometrial cancer cells. RNF8 deficiency stimulates cisplatin and doxorubicin sensitivity in endometrial cancer cells by reducing NHEJ efficiency and inducing Ku80 retention on DSBs. Knockdown of RNF8 reverses cisplatin resistance in a cisplatin-resistant mouse xenograft model [89]. BRD2, BRD3 and BRD4 were confirmed as substrates of SPOP-

CUL3. Endometrial cancer-associated SPOP mutants promote the degradation of BRD2, BRD3 and BRD4, leading to cell sensitization to BET inhibitors [90]. Moreover, USP14 a potential biomarker for stratifying patients with recurrent endometrial cancer. VLX570, an inhibitor of USP14, reduces cell proliferation via regulation of cell cycle arrest and induction of caspase-3-induced apoptosis in chemotherapy-resistant endometrial tumor cells [91]. The Skp2 E3 ligase is highly expressed in endometrial cancer cells and is accompanied by low expression of FOXO1 [92]. FBXL16 expression is upregulated and associated with MPA resistance and poor outcomes in patients with endometrial cancer. Downregulation of FBXL16 reduces the MPA tolerance of endometrial tumor cells. FBXL16 interacts with PP2A and inactivates PP2AB55α, attenuates the pAkt at Thr308, suppresses GSK-3β expression and results in reduced phosphorylation of cyclin D1at Thr286, which blocks cyclin D1 ubiquitination and degradation and MPA resistance in Ishikawa cells [93].

Compounds target ubiquitination to overcome drug resistance

Inhibitors of the proteasome

Evidence has demonstrated that compounds can overcome drug resistance via the regulation of ubiquitination in gynecological cancer. For example, ALLnL, an inhibitor of the proteasome, was reported to increase DNA platination and reduce DNA repair in ovarian cancer cells, leading to increased cisplatin toxicity in ovarian cancer cells via the inhibition of cisplatin-mediated ERCC-1 mRNA expression [94]. Lactacysin, an inhibitor of the proteasome, suppressed cisplatin-induced ERCC-1 mRNA levels in ovarian cancer cells [94]. Bortezomib, a proteasome inhibitor, increased the sensitivity of ovarian cancer cells to LDE225, a hedgehog antagonist. Bortezomib alone or in combination with LDE225 enhanced paclitaxel sensitivity via the induction of apoptosis and G2/M arrest. Bortezomib reduced the expression of ABCB1/MDR1 and increased the acetylation of α-tubulin in ovarian cancer cells. Bortezomib in combination with either carboplatin or paclitaxel exhibited synergistic effects on ovarian cancer cells [95]. Bortezomib increased the cisplatin sensitivity in ovarian cancer cells and cervical cancer cells [96, 97].

Treatment with epoxomicin, a proteasome inhibitor, in combination with cisplatin caused the accumulation of p62 and p53 in the mitochondria, resulting in impaired mitochondrial function, which induced cell apoptosis and increased cisplatin sensitivity in ovarian cancer cells [61]. Gamma-secretase inhibitors (GSI-I) were reported to repress proteasome activity in ovarian cancer cells. Bortezomib alone or in combination with the hedgehog antagonist LDE225 reduced paclitaxel resistance via the modulation of apoptosis and G2/M phase arrest. Bortezomib inhibited the expression of ABCB1/MDR1 and promoted the acetylation of α-tubulin in ovarian cancer [98].

Caffeic acid phenethyl ester

Caffeic acid phenethyl ester (CAPE) reportedly inhibits ovarian cancer growth. CAPE was found to activate proapoptotic genes and regulate EMT-related genes in A2780 ovarian cancer cells and cisplatin-resistant A2780 cells [99]. CAPE reduced the progression of ovarian cancer via inhibition of the NF-kappaB signaling pathway [100]. CAPE deregulated the expression of the Bcl2/Bax genes and enhanced cell apoptosis in serous ovarian cancer OV7 cells [101]. CAPE was observed to increase paclitaxel sensitivity in ovarian cancer cells [102]. CAPE suppressed the expression of USP8 and enhanced the efficacy of cisplatin in endometrioid ovarian carcinoma cells, including TOV112D and cisplatin-resistant IGROV-1 cells. CAPE in combination with cisplatin led to the upregulation of p27 and the accumulation of cells in the G1 phase in cisplatin-resistant IGROV-1 cells [103]. CAPE had apoptotic effects on ME180 human cervical cancer cells [104]. CAPE inhibited cell growth and induced cell cycle arrest via regulation of E2F1 in cervical cancer cells [105]. CAPE has been observed to suppress the ubiquitination and degradation of p53, leading to the activation of apoptosis-related genes and the blockade of cervical cancer cell growth. CAPE reduced E6AP expression and impaired the binding between E6AP and p53, resulting in the promotion of p53 stabilization [106].

IU1

IU1, a pharmacological compound, inhibited Dengue virus replication via suppression of USP14 [107]. IU1 has been reported to have

Table 1. Compounds target ubiquitination to overcome the drug resistance of gynecological cancer

Item	Characteristic	Mechanisms	Functions	Ref
ALLnL	Proteasome inhibitor	Inhibiting cisplatin-mediated ERCC-1 mRNA expression.	Increases DNA platination, reduces DNA repair, increases cisplatin toxicity	[94]
Lactacysin	Proteasome inhibitor	Inhibits cisplatin-induced ERCC-1 mRNA levels.	Inhibits cisplatin-induced ERCC-1 mRNA levels	[94]
Bortezomib	Proteasome inhibitor	Induction of apoptosis and G2/M arrest.	Increases paclitaxel sensitivity	[95]
Epoxomicin	Proteasome inhibitor	Accumulation of p62 and p53, impaired mitochondrial functions, induction of apoptosis.	Increases cisplatin sensitivity	[61]
GSI-I	Represses proteasome activity	Independent of Notch inhibition.	Reverses hedgehog antagonist LDE225 resistance	[98]
CAPE	A polyphenolic active ingredient in propolis	Inhibiting NF-κB, USP8, Bcl-2, E6AP, E2F1, enhances p53 stabilization, p27 expression.	Reduces E6AP, enhances p53 stabilization	[106]
IU1	Inhibits Dengue virus replication	Regulates USP14 and MDM2 degradation, inhibits AR, PI3K/AKT, Wnt.	Inhibits cell proliferation	[114]
Piceatannol	A metabolite of resveratrol	Regulates p53, XIAP, and PTEN/AKT.	Enhances cisplatin sensitivity	[121]

antitumor potential via selective inhibition of USP14 [108-110]. IU1 promoted the sensitivity of breast cancer cells to enzalutamide via downregulation of the androgen receptor (AR) and inactivation of PI3K/AKT and Wnt/β-catenin [111]. IU1 also promoted enzalutamide sensitivity in castration-resistant prostate cancer cells [112]. IU1 inhibited cell proliferation and migration by targeting USP14 in thyroid cancer cells [113]. Moreover, IU1 was found to regulate murine double minute (MDM2) degradation and inhibit cell proliferation in cervical cancer [114]. Hence, IU1 could regulate the degradation of USP14 and MDM2 in cervical cancer, leading to contribution of antitumor effects.

Piceatannol

Piceatannol, a metabolite of resveratrol, has been demonstrated to inhibit tumor development and progression [115, 116]. For instance, piceatannol inhibits tumor progression by enhancing Beclin-1 activity in gastric cancer [117]. Piceatannol activates autophagy and enhances the efficacy of immunogenic chemotherapy [118]. Piceatannol blocks the binding between VEGF and its receptors and has antiangiogenic effects [119]. Piceatannol increases cell apoptosis and represses cell proliferation by governing the PTEN/AKT signaling pathway in bladder cancer cells [120]. Piceatannol improves the effectiveness of cisplatin by altering the expression of p53 and X-linked inhibitor of apoptosis protein (XIAP) in ovarian cancer. Piceatannol promotes NOXA expression and regulates the degradation of XIAP in a ubiquitination-dependent manner in ovarian cancer cells. Piceatannol enhances cisplatin sensitivity in ovarian cancer by influencing p53, XIAP and mitochondrial fission [121].

Conclusion and future perspectives

Ubiquitination plays a critical role in modulating drug sensitivity in cervical cancer, ovarian cancer, and endometrial cancer. Numerous compounds can overcome the drug resistance by targeting ubiquitination in gynecological cancers (**Figure 2**, **Table 1**). A challenging yet promising area of research is the intricate interplay between drug resistance and ubiquitination in gynecological tumors. A potential strategy to overcome drug resistance and improve treatment outcomes by targeting ubiquitination has emerged. Several issues need to be clarified to fully understand the role of ubiquitination in regulating drug sensitivity in gynecological cancers.

First, in addition to E3 ubiquitin ligases, E2 enzymes are involved in drug resistance in gynecological cancers. Ubiquitin-conjugating enzyme E2 N (UBE2N) is decreased in ovarian cancer cells with paclitaxel resistance. Overexpression of UBE2N reduces the paclitaxel resistance of ovarian cancer cells. UBE2N governs paclitaxel sensitivity via regulation of the Fox/p53 axis in ovarian cancer [122]. HP1γ inhibits the expression of UBE2L3 and enhances p53 stability in cervical cancer cells. Leptomycin B suppresses the nuclear export of HP1γ and induces cisplatin-mediated apoptosis via activation of the p53 pathway. Doxorubicin accelerates the HP1γ-induced inhibition of UBE2L3 and enhances p53 stability [123]. Downregulation of UBE2L6 increases cisplatin sensitivity via suppression of ABCB6 transcrip-

tion [124]. Fused toes homolog (FTS), an E2 variant without ubiquitin transfer activity, promotes cisplatin resistance via suppression of EGFR-induced DNA damage repair in cervical cancer cells [125].

Second, mounting evidence has revealed that drug resistance is associated with EMT and cancer stem cells (CSCs). Because ubiquitination regulates EMT and CSCs, ubiquitination could govern drug resistance by targeting EMT and CSCs. The RNF144A E3 ubiquitin ligase targets LIN28B for ubiquitination and degradation and reduces CSC properties and malignant tumor progression in ovarian cancer [126].

Third, in addition to chemotherapeutic resistance, ubiquitination participates in the radioresistance of gynecological cancer cells. USP21 activates the Hippo signaling pathway to induce radioresistance via the deubiquitination of FOXM1 in cervical cancer cells [127]. USP21 expression was increased in radiation-treated cervical cancer cells and cervical cancer tissues with radioresistance. Depletion of USP21 increases the radio-sensitivity of cervical cancer cells via regulation of the FOXM1/Hippo pathway [127].

Fourth, the development of the MIL-88-MG132@M nanoplatform as a sequential ubiquitination and phosphorylation epigenetic regulation strategy has shown potential for overcoming drug resistance in microsatellite instability-high colorectal cancer (mCRC) patients [128, 129]. To maximize its clinical application, further investigations should expand the scope of nanoplatforms to include ovarian and cervical cancers, conduct in-depth mechanistic studies to uncover additional signaling pathways involved in drug resistance modulation, and optimize the nanoplatform's design for better therapeutic efficacy and safety.

E2 enzymes play an essential role in drug sensitivity in gynecological cancers. In the future, designing compounds that target the E2 enzyme could be an alternative approach for improving drug sensitivity in gynecological cancers. It is unclear how ubiquitination progression governs drug resistance via the regulation of EMT and CSCs. Proteolysis-targeting chimeras (PROTACs) are a novel class of therapeutic agents designed to target and destroy specific proteins [130]. Unlike traditional small molecule inhibitors that inhibit protein function, PROTACs work by harnessing their own protein degradation machinery in cells [131]. One study showed that FAK PROTAC impaired kinase-dependent and kinase-independent pathways and suppressed tumor growth and metastasis in ovarian cancer [132]. Another study reported the use of highly potent nicotinamide phosphoribosyltransferase (NAMPT) PROTACs for ovarian cancer therapy [133]. In addition, FER-targeting PROTACs were designed to antagonize ovarian cancer cell motility and invasion [134]. It is necessary to determine whether PROTACs can overcome drug resistance in ovarian cancer.

Natural compounds have been demonstrated to attenuate drug resistance by targeting ubiquitination. It is necessary to point out that natural compounds have several disadvantages associated with their use in cancer treatment, such as limited potency and specificity, complexity and variability, difficulty in isolation and purification, and poor stability. To comprehensively grasp the role of unexplored ubiquitination in drug resistance mechanisms, further in-depth research is warranted. By delving into these uncharted territories, we can gain valuable insights that may hold the key to advancing our understanding and therapeutic approaches for gynecological cancers by targeting ubiquitination.

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Disclosure of conflict of interest

None.

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