Deubiquitinating enzymes in cervical cancer: Molecular mechanisms and therapeutic implications (Review)

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Abstract. Cervical cancer (CC) remains a major global gynecological malignancy, with a rising incidence among younger women in specific regions. Human papillomavirus (HPV) screening and cytological examination have markedly reduced the disease burden; nonetheless, tumor progression, therapeutic resistance and recurrence continue to pose major clinical challenges. Thus, elucidating the molecular mechanisms underlying the progression of CC is crucial. Deubiquitinating enzymes (DUBs) regulate ubiquitin-dependent protein turnover and signaling, emerging as vital modulators of cell cycle progression, DNA damage response, apoptosis, immune regulation and HPV-associated carcinogenesis. Notably, DUBs facilitate CC progression by stabilizing oncogenic proteins, regulating tumor suppressors and modulating major signaling pathways. In addition, several DUBs are closely associated with radiosensitivity, chemoresistance and potential targeted therapeutic strategies. The present review summarizes the molecular mechanisms and therapeutic implications of DUBs in CC, while discussing their translational value for future clinical applications.

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Contents

1. Introduction

Cervical cancer (CC) ranks among the most prevalent gynecological malignancies, constituting a persistent and substantial global health challenge (1). While advances in human papillomavirus (HPV) screening and vaccination have improved prevention and early detection, a notable number of patients still experience delayed diagnosis, treatment resistance, recurrence and poor clinical outcomes. Thus, elucidating the molecular mechanisms that underlie CC initiation and progression is fundamental to improving disease management and refining therapeutic strategies (2).

Ubiquitination and deubiquitination are essential processes for maintaining cellular function and homeostasis (3). Ubiquitination is regulated by a coordinated enzymatic cascade involving ubiquitin-activating enzyme E1, ubiquitin-conjugating enzyme E2 and ubiquitin ligase E3 (3). This process is reversed by deubiquitination, which is mediated by deubiquitinating enzymes (DUBs) (3). Notably, >100 DUBs have thus far been identified and classified into nine superfamilies based on sequence and structural features (Fig. 1): Ubiquitin-specific peptidase (USP), ovarian tumor-related protease (OTU), ubiquitin C-terminal hydrolase (UCH), Machado-Joseph domain-containing protease (MJD), JAMM/MPN domain-associated (JAMM/MPN) metallopeptidase, motif-interacting with ubiquitin-containing novel DUB (MINDY), monocyte chemotactic protein-induced protein (MCPIP), permuted papain fold peptidases of dsRNA

viruses and eukaryotes (PPPDE) and zinc finger-containing ubiquitin peptidase 1 (ZUP1) families (3). A subgroup termed pseudo-DUBs has been proposed to describe DUB family members that lack canonical catalytic activity because of defects in key residues or domains (4). However, subsequent studies have suggested that this classification is not absolute. Several proteins previously categorized as pseudo-DUBs, including USP39 (5), USP53 (6), USP54 (6), PSMD7 (7), eukaryotic translation initiation factor 3 subunit F (EIF3F) (8) and STAMBPL1 (9), retain or exhibit deubiquitinating activity under specific conditions. Enzymatic activity has also been confirmed for PPPDE1 (10), MCPIP1 (11) and MCPIP4 (12). These findings indicate that the classification of pseudo-DUBs is dynamic and should be interpreted cautiously as functional evidence continues to emerge.

DUBs function by recognizing ubiquitin-tagged proteins and hydrolyzing isopeptide bonds between ubiquitin molecules, or between ubiquitin and substrate proteins. Through these actions, DUBs regulate cell cycle progression, DNA damage repair, apoptosis, immune regulation and signal transduction, among other cellular events (13,14). Growing evidence has shown that dysregulated DUB activity contributes to the development and progression of various malignancies, including gynecologic cancer (15-17). Although several studies have examined DUBs in CC (13,15,18), a comprehensive review of their molecular functions, regulatory mechanisms and therapeutic relevance is lacking. The present review systematically summarizes current research on DUBs in CC, with emphasis on their roles in HPV-associated carcinogenesis, signaling pathway regulation, tumor progression, therapy response and potential DUB-targeted therapies.

2. USPs: Key regulatory factors in the development and progression of CC

The USP family is the largest subgroup of DUBs, with >50 members that account for ~60% of all DUBs. USPs are mainly involved in cell cycle regulation, DNA damage repair and chromatin repair, thereby affecting various cellular functions and leading to disease progression. Notably, >50 USP family members have been implicated in the onset, progression and treatment of cancer (18-20).

USP3. USP3 is a cysteine protease and one of the few known members of the USP family capable of efficiently cleaving the ubiquitin-proline bond (21). Data from The Cancer Genome Atlas (TCGA) have indicated that high USP3 expression is associated with poor survival in adrenocortical carcinoma, breast cancer and pancreatic adenocarcinoma, whereas elevated USP3 expression predicts better survival in two brain tumor types, including low-grade glioma and glioblastoma (21). No statistically significant difference in USP3 expression has been observed in CC. Studies have also demonstrated that USP3 is closely associated with DNA damage response (DDR), cell cycle regulation, apoptosis and immune regulation (22-24). Evidence has suggested that USP3 regulates the cell cycle by stabilizing the cell division cycle 25A (Cdc25A) protein through deubiquitination, and this process is implicated in cancer development and progression. A previous mechanistic study indicated that USP3 expression is positively associated with Cdc25A protein levels; knockdown of USP3 can reduce Cdc25A protein levels, thereby inhibiting the G_1-to-S phase transition and suppressing tumor growth in xenograft models established using USP3-depleted or -overexpressing HeLa cells (21). Additionally, USP3 and Cdc25A have been shown to co-localize and interact within the nucleus, where USP3 extends the half-life of Cdc25A via deubiquitination, ensuring its stability throughout the cell cycle (21). Analysis of TCGA database has revealed that USP3 and Cdc25A are upregulated in multiple cancer types. Clinically, elevated expression of USP3 and Cdc25A has been associated with poor prognosis in breast cancer, supporting a pro-tumorigenic role for this axis in certain types of cancer (21). However, TCGA data have shown no notable difference in USP3 expression between patients with CC (n=305) and healthy normal controls, suggesting that its clinical relevance varies across tumor types (http://gepia.cancer-pku.cn/detail.php?gene=USP3###) (25). Collectively, these findings identify USP3 as a functionally important DUB in oncogenesis and support the USP3/Cdc25A axis as a potential therapeutic target, although its cancer-type-specific importance requires further investigation.

USP7. USP7, also known as herpesvirus-associated ubiquitin-specific protease, is one of the most extensively studied DUBs (26). Recent studies have shown that USP7 is associated with various types of cancer, including glioblastoma (27), breast cancer (28), colorectal cancer (29) and ovarian cancer (30). In CC, USP7 is consistently upregulated and is associated with malignant progression; notably, increased USP7 expression is associated with advanced histological grade and poor patient prognosis (31,32).

Functionally, USP7 promotes oncogenic phenotypes in CC, including increased proliferation, migration, invasion, angiogenesis, immune evasion and resistance to DNA damage, through several distinct but complementary molecular mechanisms. In the DDR, USP7 interacts with the MRE11-RAD50-NBS1 (MRN) complex and mediator of DNA damage checkpoint protein 1 (MDC1), stabilizing the MRN-MDC1 complex through MDC1 deubiquitination. This stabilization facilitates recruitment of key DDR factors, such as 53BP1 and BRCA1 to DNA double-strand breaks. Loss of USP7 disrupts this process, impairs DDR and increases CC cell sensitivity to DNA damage (31). USP7 also promotes tumor progression by deubiquitinating and stabilizing metadherin (MTDH), enhancing proliferation, migration, invasion, angiogenesis and M2 macrophage polarization. Silencing USP7 reduces MTDH levels, inhibits tumor progression and promotes apoptosis (32). In addition, USP7 stabilizes Cdc25A through deubiquitination, protecting it from DDR-induced degradation and sustaining CC cell proliferation. In HeLa cells, USP7 knockout has been shown to markedly impair Cdc25A-dependent proliferation, migration and colony formation, reduce xenograft tumor growth, and increase sensitivity to etoposide, hydroxyurea and ultraviolet radiation (33). Moreover, USP7 regulates the EZH2/TIMP2/NF-κB/PD-L1 signaling axis. USP7-mediated upregulation of EZH2 suppresses TIMP2 through methylation, activates NF-κB signaling and increases PD-L1 expression, thus promoting immune escape, tumor growth and metastasis (34). Clinically, elevated USP7 expression is associated with aggressive clinicopathological

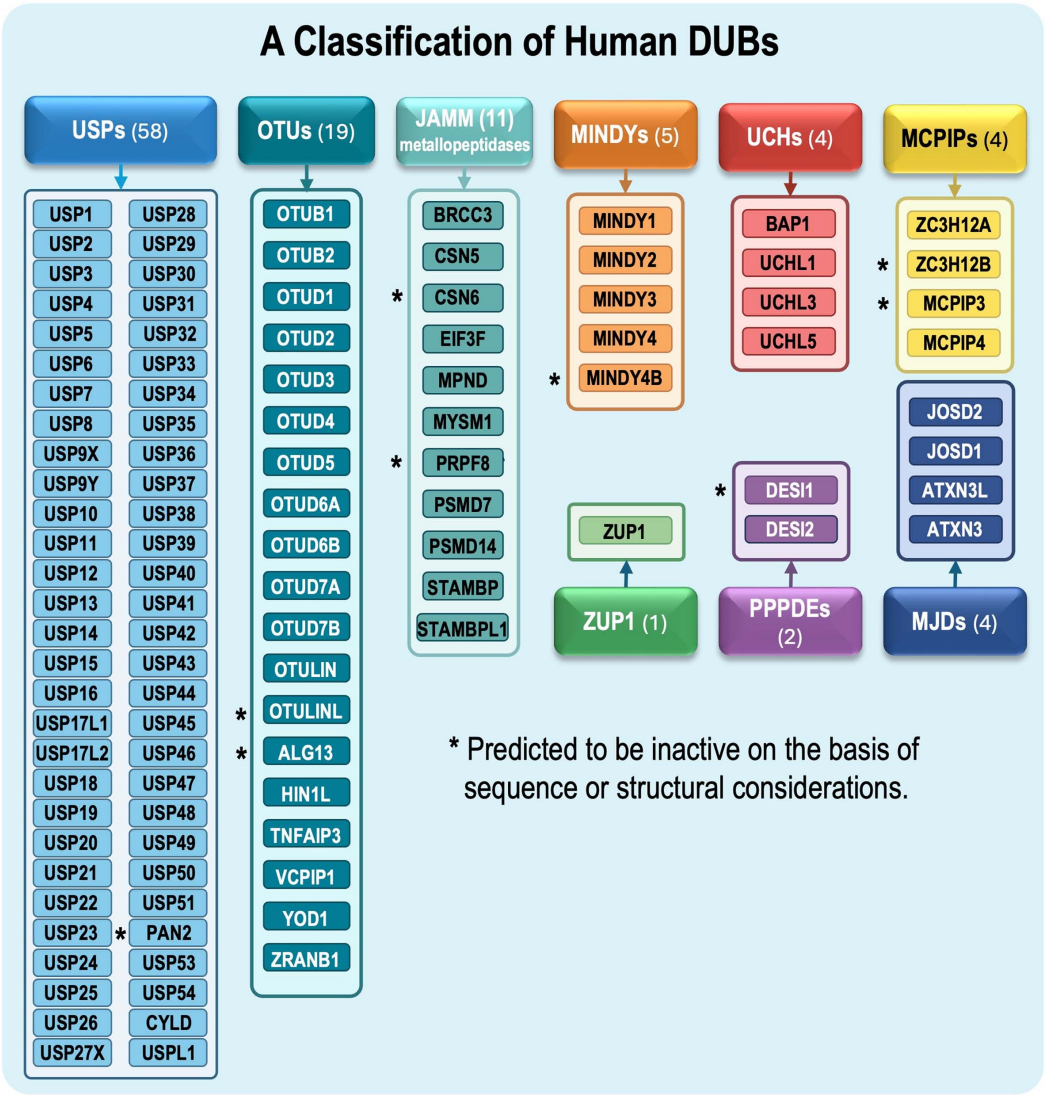

Figure 1. Classification of human DUBs. Human DUBs are classified into cysteine protease or metallopeptidase families based on their sequence and structural features. The largest family comprises 58 USPs, followed by 19 OTUs and 9 JAMM metallopeptidases. Additional cysteine protease families include 5 MINDY proteins, 4 UCHs, 4 MCPIP-related proteins, 4 MJDs, 2 PPPDEs and ZUP1. Individual family members are listed within each colored box. Proteins marked with an asterisk are predicted to lack catalytic activity based on their amino-acid sequence analysis or structural evidence. DUB, deubiquitinating enzyme; JAMM metallopeptidase, JAMM/MPN domain-associated metallopeptidase; MCPIP, monocyte chemotactic protein-induced protein; MINDY, motif-interacting with ubiquitin-containing novel DUB; MJD, Machado-Joseph domain-containing protease; OTU, ovarian tumor-related protease; PPPDE, permuted papain fold peptidase of dsRNA viruses and eukaryotes; UCH, ubiquitin C-terminal hydrolase; USP, ubiquitin-specific peptidase; ZUP1, zinc finger-containing ubiquitin peptidase 1.

features and poor prognosis in CC, supporting its value as a potential biomarker.

Collectively, these findings demonstrate the multifaceted oncogenic role of USP7 in CC and highlight several therapeutically actionable pathways, including the USP7/MDC1, USP7/MTDH, USP7/Cdc25A and USP7/EZH2/TIMP2/NF-κB/PD-L1 axes. Targeting USP7 may thus represent a promising strategy to sensitize CC cells to DNA-damaging agents and suppress tumor progression.

USP8. USP8 is a multifunctional DUB involved in mitophagy, autophagy, cell cycle regulation, apoptosis and the DDR (35). Evidence has demonstrated that USP8 is highly expressed in CC tissues relative to normal cervical tissues; this elevation is particularly pronounced in cervical squamous cell carcinoma (CSCC), and has been validated at both the mRNA and protein levels (36,37). Functionally, USP8 exerts oncogenic effects by promoting tumor cell proliferation, migration, invasion, survival and overall tumor growth (36,37). Mechanistically, USP8 deubiquitinates and stabilizes FLICE-like inhibitory protein (FLIPL), thereby suppressing extrinsic apoptosis induced by Fas, TRAIL and TNF-α, and facilitating tumor progression (37). Consistent with these findings, USP8 inhibition has been shown to markedly reduce tumor volume and weight in xenograft models, further supporting its tumor-promoting role (37). Clinically, elevated USP8 expression is closely associated with advanced tumor stage, poor prognosis and reduced overall survival in patients with CSCC, indicating its potential as a prognostic biomarker (36). Collectively, these findings underscore the therapeutic potential of USP8 in CC and suggest that targeting the USP8/FLIPL axis may effectively attenuate tumor progression and improve patient outcomes.

USP11. USP11 is a key member of the largest subfamily of cysteine protease DUBs (38). It is widely distributed in the nuclei of mitotic cells, consistent with its role in nuclear events related to cell proliferation and genome maintenance (39,40). In CC, its oncogenic relevance is closely linked to HPV, particularly the HPV-16 E7 oncoprotein, the stability of which is essential for its transforming activity. Mechanistically, USP11 stabilizes HPV-16 E7 by reducing its ubiquitination and preventing proteasomal degradation; this effect depends on its DUB activity, as a catalytically inactive USP11 mutant has been reported to fail to protect E7 and restore its normal degradation rate (41). USP11-mediated stabilization of HPV-16 E7 also affects downstream targets, including pRb, Bcl-2 and Cdc2, thereby promoting CC cell proliferation and transformation (41). These findings indicate that USP11 may contribute to cervical carcinogenesis by sustaining HPV-16 E7 stability and oncogenic function. Targeting USP11 could therefore destabilize HPV-16 E7, and inhibit CC cell proliferation and transformation.

USP14. USP14 is aberrantly expressed in several gynecological diseases, including deep infiltrating endometriosis (42), premature ovarian failure (43) and endometrial cancer (44). Evidence has suggested that USP14 contributes to CC progression, although its expression pattern in CC remains incompletely defined. Functionally, USP14 promotes CC cell proliferation, and regulates cell cycle progression and survival (45). Mechanistically, USP14 facilitates proliferation through modulating the protein stability of murine double minute protein 2 (MDM2). Pharmacological inhibition of USP14 by IU1 can reduce MDM2 expression, activate the autophagy-lysosome degradation pathway, enhance ubiquitin-proteasome system activity, block the G_0/G_1-to-S transition and induce apoptosis (45). These findings suggest that USP14 supports tumor cell proliferation and contributes to disease progression. Targeting the USP14/MDM2 axis or developing USP14 inhibitors may therefore represent a promising therapeutic strategy.

USP15. USP15 contributes to disease initiation and progression through DNA damage repair (46), regulation of tumor-related signaling pathways (47) and modulation of immune responses (48). In CC, evidence mainly reflects functional regulation of USP15 rather than a clearly defined expression pattern. Under hypoxic conditions, microRNA (miRNA/miR)-100 is markedly upregulated in CC cells and directly suppresses USP15 translation, reducing USP15 mRNA and protein levels (49). Functionally, USP15 supports viral oncoprotein stability and influences chemotherapeutic response. Mechanistically, USP15 interacts with the HPV-16 E6 oncoprotein and prevents its degradation through deubiquitination, thereby stabilizing E6 protein levels, enhancing its oncogenic activity and promoting CC cell proliferation (50). USP15 is also linked to paclitaxel resistance. Hypoxia-induced miR-100 downregulates USP15 and contributes to induced drug responsiveness in CC cells (49,51). Clinically, these findings suggest that USP15 participates in both HPV-driven carcinogenesis and chemotherapy resistance, although its clinical relevance remains limited and evidence for paclitaxel resistance is currently restricted to an *in vitro* study (49). Collectively, these observations highlight the therapeutic potential of USP15 in CC. Targeting USP15, its DUB activity toward HPV-16 E6 or its regulatory interaction with miR-100 may offer promising treatment strategies.

USP17. USP17 comprises a family of structurally related proteins (52). Aberrant USP17 expression has been implicated in several diseases, including preeclampsia (53), colorectal cancer (54) and lung adenocarcinoma (55), suggesting a context-dependent role in human pathophysiology. With regard to biological function, available evidence has indicated that USP17 exerts tumor-suppressive effects in CC by promoting apoptosis, and inhibiting cell proliferation and cell cycle progression. At the molecular level, USP17 induces apoptosis and suppresses proliferation of cervical adenocarcinoma cells through Lys63-specific deubiquitination of suppressor of defective silencing 3 (SDS3), a component of histone deacetylase (HDAC)-dependent Sin3A co-repressor complex, thereby negatively regulating HCAC activity (56). USP17 also inhibits the localization of H-Ras and N-Ras, but not K-Ras, to the plasma membrane, attenuating MEK/ERK and PI3K/JNK signaling, and leading to cell cycle arrest (57). These findings suggest that USP17 may function as a negative regulator of CC progression. Modulation of the USP17/SDS3/HDAC and USP17/Ras axes could therefore represent a potential therapeutic strategy, although further studies are required to clarify its mechanisms and translational relevance.

USP18. USP18 regulates immune responses and cell death, particularly through the type I interferon pathway, which has been implicated in tumor development via induction of immunogenic cell death (58,59). USP18 is markedly upregulated in CC tissues and cell lines (60). With regard to biological function, USP18 promotes CC cell proliferation and suppresses apoptosis, indicating a pro-tumorigenic role (60). At the molecular level, USP18 is associated with the PI3K/AKT signaling pathway. The oncogenic effects of USP18 upregulation are markedly reduced by the PI3K/AKT inhibitor LY294002, suggesting that USP18 promotes tumor progression at least partly through activation of PI3K/AKT signaling (60). Elevated USP18 expression may therefore contribute to disease progression and serve as a biomarker of malignant behavior, and targeting USP18 alone or in combination with PI3K/AKT pathway inhibition may represent a promising therapeutic strategy.

USP19. USP19 serves a context-dependent role in tumor progression, exhibiting tumor-promoting or tumor-suppressive effects depending on cellular context (61). Dysregulated USP19 expression has been associated with CC progression. Functionally, USP19 promotes CC cell proliferation, migration and invasion. At the molecular level, USP19 directly interacts with the tumor suppressor p53 and enhances its ubiquitination and degradation, thereby reducing p53 stability (62). Because p53 is a key regulator of the DDR (63) and its loss is closely linked to malignant progression, USP19-mediated suppression of p53 provides a mechanistic basis for CC development. CRISPR/Cas9-mediated USP19 knockout has been shown to markedly increase p53 levels and inhibit malignant behavior in CC cells (62). Clinically, these findings indicate that USP19 contributes to CC aggressiveness through modulation of the

p53 signaling axis. Accordingly, the USP19/p53 axis may serve as a biomarker and therapeutic target for precision treatment in CC.

USP21. USP21 has been implicated in tumor progression through its roles in cell signaling, DNA damage and repair, and histone modification (64). Elevated USP21 expression is positively associated with radioresistance in CC tissues (65). Functionally, USP21 promotes radioresistance and inhibits apoptosis, whereas its knockdown enhances radiosensitivity and induces apoptosis in CC cells (65). At the molecular level, USP21 regulates the stability of the transcription factor FOXM1; silencing USP21 may reduce FOXM1 stability, inhibit YAP1 nuclear translocation and activate Hippo signaling, ultimately increasing CC cell sensitivity to radiotherapy (65). Activation of Hippo signaling promotes apoptosis and enhances radiosensitivity. Consistently, USP21 knockdown has been reported to promote apoptosis, increase radiosensitivity and suppress xenograft tumor growth (65). These findings indicate that USP21 contributes to treatment resistance and disease progression in CC. Accordingly, the USP21/FOXM1/Hippo axis may serve as a biomarker and therapeutic target for improving radiosensitivity in CC.

USP22. USP22 functions as an oncogenic DUB in several malignancies, including lung, breast, ovarian and liver cancer, by regulating cell cycle progression, signal transduction and immune responses (66). USP22 is also highly expressed in CC (67). Although its specific biological functions and molecular mechanisms in CC remain unclear, evidence from other cancer types suggests that USP22 contributes to tumor progression through oncogenic activity (66,67). Clinically, elevated USP22 expression in CC is markedly associated with adverse clinicopathological parameters, including advanced International Federation of Gynecology and Obstetrics (FIGO) stage, high Ki67 index, lymph node metastasis and poor histological differentiation (67). In addition, patients with CC and high USP22 expression exhibit significantly reduced overall survival and disease-free survival compared with those with low expression ($P<0.001$) (67). Collectively, these findings indicate that USP22 may serve as a prognostic biomarker, and an auxiliary indicator for guiding systemic treatment and predicting therapeutic outcomes in CC.

USP26. USP26 was initially identified in mouse spermatogonia and linked to male infertility, but has since been implicated in cancer progression and bone homeostasis (68). Its expression pattern in CC remains incompletely defined, although functional evidence suggests a tumor-suppressive role (15). Ye *et al* (15) demonstrated that USP26 can inhibit CC cell proliferation and migration. At the molecular level, this effect is mediated through the deubiquitination and stabilization of Krüppel-like factor 6 (KLF6), a transcription factor that regulates cell cycle progression and promotes apoptosis, and is widely recognized as a tumor suppressor in several malignancies, including prostate and breast cancer (15,69). By maintaining KLF6 protein stability, USP26 suppresses malignant behavior in CC cells (15). These findings indicate that USP26 expression is associated with a less aggressive CC phenotype and the USP26/KLF6 axis may represent a potential therapeutic target; however, further clinical studies are needed to clarify its expression pattern and prognostic value.

USP39. USP39 is aberrantly expressed in several malignancies, including gastric, colorectal and endometrial cancer, and it contributes to tumor progression (70). In CC, USP39 is highly expressed in both tissues and cell lines (71). Functionally, USP39 promotes proliferation, survival, autophagy and oxidative stress responses in CSCC cells (71). At the molecular level, sirtuin7 (SIRT7) interacts with and deacetylates USP39, enhancing its protein stability (71). USP39 then regulates alternative splicing of FOXM1 pre-mRNA and upregulates SIRT7 expression; subsequently, SIRT7 positively regulates USP39 and FOXM1, establishing a positive feedback loop that sustains malignant progression (71). Elevated USP39 expression is associated with CC progression and aggressiveness (71). The SIRT7/USP39/FOXM1 axis may thus represent a potential therapeutic target.

USP45. USP45 exhibits oncogenic DUB activity; however, its precise role in tumorigenesis has not been fully elucidated (72). USP45 is upregulated in tumors and highly expressed in CC cells (72,73). Functionally, USP45 promotes CC cell proliferation, stemness and drug resistance (73). At the molecular level, USP45 stabilizes Myc through deubiquitination, thereby enhancing proliferative capacity and stem cell-like properties in CC cells (73). Clinically, elevated USP45 expression is negatively associated with overall survival and recurrence-free survival, indicating its potential value as a prognostic marker (72). Targeting the USP45/Myc axis may thus represent a promising therapeutic strategy. Notably, α-mangostin has been identified as a specific USP45 inhibitor that suppresses proliferation and reduces drug resistance in CC cells (73). Collectively, these findings support an oncogenic role for USP45 in CC and highlight its potential as a therapeutic target.

USP53. USP53 is broadly expressed in human tissues and has been reported to function as a tumor suppressor in several types of cancer, including lung, colorectal and liver malignancies (74). In CC, USP53 expression is associated with radiosensitivity; functionally, USP53 enhances the response of CC cells to radiotherapy (75). At the molecular level, USP53 interacts with DNA damage-binding protein 2 (DDB2) and upregulates its expression, promoting nucleotide excision repair and increasing DNA repair capacity (75). USP53 also induces G_2/M arrest, and alters CDK1 and CDK2 expression, which may further contribute to radiosensitization (75). These findings identify USP53 as a predictive biomarker for radiotherapy response and a potential target for radiosensitization strategies in CC.

CYLD. CYLD is a well-established tumor suppressor that regulates cell cycle progression, signal transduction and DDR, and its dysregulation is frequently linked to malignant progression (76). In CC, CYLD expression is significantly downregulated and negatively associated with miR-501 levels (77). Reduced CYLD expression is also associated with enhanced Aurora B activation and increased histological invasiveness in advanced CC specimens (78). Functionally, CYLD inhibits CC cell proliferation, migration, invasion and colony

formation while promoting apoptosis (77,78). Mechanistically, miR-501-mediated repression of CYLD contributes to malignant phenotypes and apoptosis resistance, possibly through activation of NF-κB p65 signaling, upregulation of Bcl-2 and downregulation of Bax (77). CYLD also directly deubiquitinates Aurora B, suppressing its activation and mitotic function, delaying mitosis and inhibiting CC development (78). Clinically, low CYLD expression is significantly associated with large tumor size, advanced FIGO stage, lymph node metastasis, heightened Aurora B activity and increased histological invasiveness (77,78). These findings support CYLD as both a prognostic biomarker and a potential therapeutic target in CC (77,78).

The USP family serves a broad and complex role in CC and appears to function as an integrated regulatory system connecting viral oncogenesis, cell cycle control, DDR, aberrant signaling and immune evasion (Fig. 2; Table I). Most USP members reported in CC, including USP3, USP7, USP8, USP11, USP14, USP15, USP18, USP19, USP21, USP22, USP39 and USP45, generally show tumor-promoting functions. These proteins enhance cell proliferation, migration, invasion, angiogenesis and immune escape, and contribute to resistance to radiotherapy and chemotherapy. Mechanistically, these effects are mediated through stabilization of oncogenic substrates, suppression of tumor suppressor turnover, activation of key signaling pathways such as PI3K/AKT, Wnt/β-catenin, NF-κB, and RAS/MAPK, and modulation of HPV-16 E6/E7 oncogenic functions. By contrast, several members, including USP17, USP26, USP53 and CYLD, exhibit tumor-suppressive or radiosensitizing effects in specific contexts, highlighting the context-dependent nature of USP-mediated regulation in CC. Clinically, dysregulated USP expression is associated with FIGO stage, lymph node metastasis, tumor burden, prognosis and treatment response, supporting their potential use as biomarkers. In addition, advances in small-molecule inhibitors and deubiquitinase-targeting chimera (DUBTAC)-based approaches suggest that targeting selected USPs may be a feasible strategy for precision therapy. Taken together, the USP family represents not only an important contributor to CC progression, but also a potentially valuable source of diagnostic, prognostic and therapeutic targets.

3. UCHs: Potential targets and mechanisms in the diagnosis and treatment of CC

At present, the human UCH subfamily contains only four members, namely UCHL1, UCHL3, UCHL5 and BRCA1-associated protein-1 (BAP1). The primary function of UCHs is to hydrolyze the isopeptide bonds at the C-terminus of protein substrates. Research has increasingly highlighted the role of UCHs in malignant tumors, especially in gynecological malignancies, breast cancer and liver cancer (79,80).

UCHL1. UCHL1 is a DUB involved in protein degradation, cell cycle control and apoptosis, and exhibits context-dependent roles in cancer (80,81). In CC, UCHL1 is highly expressed in both CSCC and small cell neuroendocrine carcinoma (SCNEC) (82,83). Functionally, UCHL1 promotes proliferation, migration and invasion in CSCC, and is associated with increased metastatic potential in SCNEC (82,83). Mechanistically, UCHL1 reduces prospero homeobox 1 (PROX1) ubiquitination, stabilizing this transcription factor, and promoting migration, invasion and lymph node metastasis, particularly in SCNEC (83). Clinically, elevated UCHL1 expression is associated with poor prognosis and reduced overall survival in CSCC, and increased lymph node metastasis in SCNEC (82,83). These findings suggest that UCHL1 functions as a context-dependent oncogenic regulator, and exhibits potential as a prognostic biomarker and a therapeutic target.

UCHL3. UCHL3 regulates cell cycle progression, apoptosis and DNA damage repair, and has tumor-promoting roles in several cancer types, including liver, bladder and ovarian cancer (84,85). In CC, UCHL3 is highly expressed and its expression is negatively associated with patient survival (85). A cell-based study has shown that UCHL3 promotes CC cell proliferation, migration and invasion (85), whereas an *in vivo* study demonstrated that UCHL3 knockdown suppresses tumor growth and reduces lung metastasis in mouse models (85). Mechanistically, UCHL3 stabilizes nuclear factor erythroid 2-related factor 2 (NRF2) through deubiquitination, increasing NRF2 levels and enhancing downstream oncogenic effects. A catalytically inactive UCHL3 (C92A) mutant fails to stabilize NRF2, indicating that this effect depends on its deubiquitinating activity (85). Clinically, elevated UCHL3 expression is associated with poor prognosis in patients with CC, highlighting its potential relevance as a prognostic biomarker. These findings suggest that the UCHL3/NRF2 axis serves a critical role in CC progression and may represent a promising therapeutic target.

UCHL5. UCHL5 (also known as UCH37) is a conserved DUB that is aberrantly expressed in multiple types of cancer and often exhibits oncogenic activity, although its prognostic importance is tumor type-dependent (86,87). In CC, UCHL5 is markedly upregulated in tumor tissues, and is closely associated with tumor stage and patient prognosis (88,89). Functionally, UCHL5 promotes CC cell proliferation and migration while suppressing apoptosis (89,90). Mechanistically, UCHL5 regulates the Wnt/β-catenin signaling pathway by reducing β-catenin ubiquitination and preventing its proteasomal degradation, thereby maintaining c-Myc expression and promoting malignant progression (89,90). As a proteasome-associated DUB, UCH37 also contributes to proteasomal homeostasis by facilitating Rpn13 recruitment and reversing the ubiquitination of key substrates (90). Clinically, UCHL5 expression is associated with patient prognosis and features of the tumor immune microenvironment, suggesting a role in disease progression and immunotherapy response (90). These findings support UCHL5 as a prognostic biomarker and potential therapeutic target in CC, particularly through modulation of the Wnt/β-catenin signaling axis.

BAP1. BAP1 is an important DUB involved in cell cycle regulation, DNA damage repair and apoptosis, and generally functions as a tumor suppressor in multiple types of cancer (91,92). In CC, BAP1 has been identified as a direct target of miR-31, an oncogenic miRNA that is highly expressed

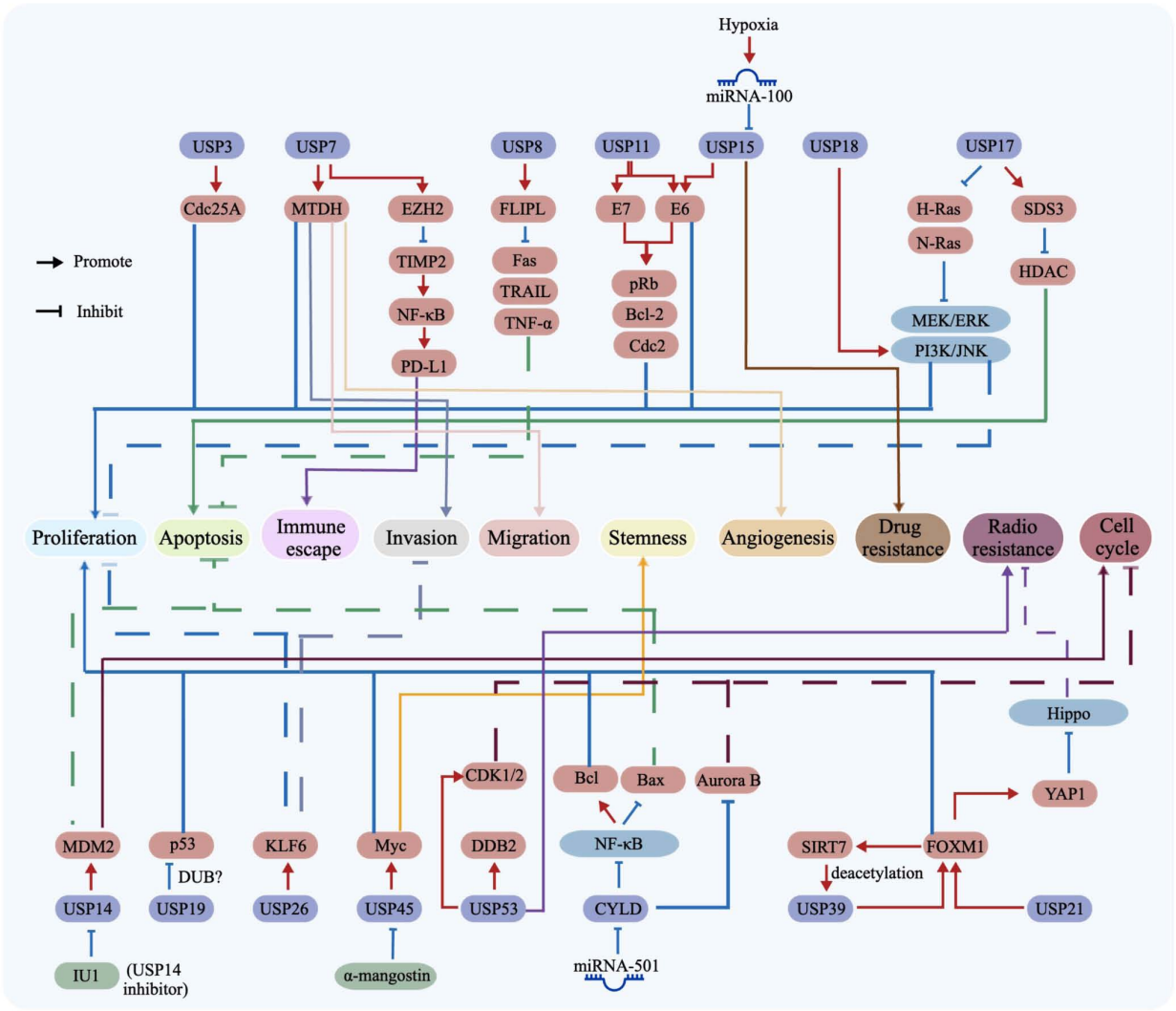

Figure 2. Regulatory network of USPs in tumor progression and therapy resistance. Schematic diagram illustrating the roles of multiple USPs and their downstream targets in regulating malignant phenotypes in CC. USP3, USP7, USP8, USP11, USP15, USP17, USP18, USP19, USP21, USP26, USP39, USP45, USP53 and CYLD modulate diverse oncogenic or tumor-suppressive pathways through substrates or signaling mediators including Cdc25A, MTDH, EZH2, TIMP2, NF-κB, PD-L1, Fas, TRAIL, TNF-α, HPV E6/E7, pRb, Bcl-2, Cdc2, Ras, HDAC, MEK/ERK, PI3K/JNK, MDM2, p53, KLF6, Myc, CDK1/2, DDB2, Bax, Aurora B, SIRT7, FOXM1, and YAP1. These signaling events converge on key cancer-associated processes, including proliferation, apoptosis, immune escape, invasion, migration, stemness, angiogenesis, drug resistance, radioresistance and cell cycle regulation. The influence of non-coding RNAs and microenvironmental cues, such as hypoxia/miRNA-100 and miRNA-501, as well as small molecule modulators, including α-mangostin and IU1, on USP-centered signaling networks are also highlighted. Arrows indicate activation or positive regulation, whereas blunt-ended lines indicate inhibition or negative regulation. Overall, the diagram emphasizes the central role of USP-mediated deubiquitination in coordinating tumor progression, cellular adaptation and therapeutic response in CC. CC, cervical cancer; Cdc, cell division cycle; DDB2, DNA damage-binding protein 2; DUB, deubiquitinating enzyme; FLIPL, FLICE-like inhibitory protein; HDAC, histone deacetylase; HPV, human papillomavirus; KLF6, Krüppel-like factor 6; MDM2, murine double minute protein 2; miRNA, microRNA; MTDH, metadherin; SDS3, HDAC-dependent Sin3A co-repressor complex; USP, ubiquitin-specific protease.

in CC cells and tissues (93). Functionally, miR-31 promotes CC cell proliferation, epithelial-mesenchymal transition (EMT) and tumor growth *in vivo*, suggesting that suppression of BAP1 contributes to CC progression (93). Mechanistically, miR-31 directly inhibits BAP1 expression, weakening its tumor-suppressive activity and facilitating malignant phenotypes (93). Clinically, elevated miR-31 expression is associated with lymph node metastasis, stromal invasion, lymphovascular space invasion, advanced FIGO stage, larger tumor size and poor prognosis (93). These findings highlight the clinical relevance of the miR-31/BAP1 axis and suggest that it may serve as a potential therapeutic target.

In summary, the UCH family predominantly exhibits tumor-promoting roles in CC, although functional diversity exists among individual members. Biologically, UCH proteins regulate protein stability and ubiquitin-dependent signaling, influencing malignant phenotypes such as proliferation, migration, invasion, apoptosis, EMT, DDR and metastasis. Mechanistically, these effects involve key substrates and pathways, including PROX1, NRF2, BAP1 and the Wnt/β-catenin/c-Myc axis (Fig. 3; Table I). Clinically, aberrant expression of UCH family members is strongly associated with tumor progression, lymph node metastasis and poor patient survival across various CC subtypes. These associations underscore their potential as biomarkers for prognostic stratification and metastatic risk assessment. UCH proteins may also represent promising therapeutic targets. However, existing data are limited, necessitating further studies to clarify the context-dependent functions of individual UCH

Table I. List of DUBs, their substrates and functions associated with CC.

First author, year	DUB	Expression of level in CC	Substrates or related proteins	Role of DUB	Mechanisms and functions	(Refs.)
Das, 2020	USP3	High expression	Cdc25A	Stabilizes protein structure	USP3 promotes CC progression by regulating cell cycle progression by deubiquitinating Cdc25A	(21)
Su, 2018	USP7	High expression	MDC1	Stabilizes protein structure	USP7 enhances the DDR by deubiquitinating MDC1, thus affecting accumulation of the MRN-MDC1 complex and promoting CC development	(31)
Wang, 2024	USP7	High expression	MTDH	Stabilizes protein structure	USP7 promotes CC progression by deubiquitinating MTDH	(32)
Das, 2020	USP7	Not mentioned	Cdc25A	Stabilizes protein structure	USP7 promotes CC development by deubiquitinating Cdc25A	(33)
Li, 2022	USP7	High expression	EZH2, TIMP2	Mediates signal transduction	USP7 promotes immune escape by upregulating EZH2; EZH2 inhibits TIMP2 to activate NF-κB signaling and increase PD-L1 expression	(34)
Jeong, 2017	USP8	High expression	FLIPL, Fas, TRAIL, TNF-α	Stabilizes protein structure	USP8 promotes CC progression by deubiquitinating FLIPL and inhibiting apoptosis	(37)
Lin, 2008	USP11	Not mentioned	HPV-16 E7	Stabilizes protein structure	USP11 promotes CC progression by deubiquitinating HPV-16 E7	(41)
Xu, 2020	USP14	Not mentioned	MDM2	Stabilizes protein structure	USP14 promotes CC progression by deubiquitinating MDM2	(45)
Yaginuma, 2018	USP15	Not mentioned	HPV-16 E6	Stabilizes protein structure	USP15 promotes CC progression by deubiquitinating HPV-16 E6	(50)
Yu, 2024	USP15	Not mentioned	miR-100	Downstream factor	Hypoxia upregulates miR-100 expression, reduces USP15 levels, and thereby induces chemoresistance in CC	(51)
Ramakrishna, 2011	USP17	Not mentioned	SDS3, HDAC	Stabilizes protein structure	USP17 inhibits cell apoptosis by regulating the activities of SDS3 and HDAC	(56)
de la Vega, 2010	USP17	Not mentioned	Ras, N-Ras	Mediates signal transduction	USP17 suppresses CC progression by inhibiting the localization of H-Ras and N-Ras to the plasma membrane, leading to the downregulation of MAPK, MEK/ERK, and PI3K/JNK signaling pathways	(57)
Diao, 2020	USP18	High expression	PI3K/AKT	Mediates signal transduction	USP18 promotes CC progression through the PI3K/AKT signaling pathway	(60)
Tyagi, 2024	USP19	Not mentioned	p53	Stabilizes protein structure	USP19 promotes CC progression by deubiquitinating p53	(62)
Li, 2022	USP21	Not mentioned	FOXM1	Stabilizes protein structure and mediates signal transduction	USP21 deubiquitinates FOXM1 to mediate the Hippo signaling pathway, thereby affecting radiotherapy resistance and promoting the progression of CC	(65)
Ye, 2024	USP26	Not mentioned	KLF6	Stabilizes protein structure	USP26 inhibits CC progression by deubiquitinating KLF6	(15)
Yu, 2023	USP39	High expression	SIRT7, FOXM1	Stabilizes protein structure	USP39 promotes CC progression through interaction with SIRT7 and FOXM1	(71)

Table I. Continued.

First author, year	DUB	Expression of level in CC	Substrates or related proteins	Role of DUB	Mechanisms and functions	(Refs.)
Tu, 2023	USP45	High expression	Myc	Stabilizes protein structure	USP45 promotes chemoresistance and progression of CC by deubiquitinating Myc	(73)
Zhou, 2020	USP53	Not mentioned	DDB2	Stabilizes protein structure	USP53 promotes radiosensitivity in CC by mediating DDR through interaction with DDB2	(75)
Sanches, 2018	CYLD	Low expression	miR-501	Downstream factor and mediates signal transduction	miR-501 inhibits CYLD expression, thereby activating the NF-κB signaling pathway and promoting CC progression	(77)
Huang, 2023	CYLD	Not mentioned	Aurora B	Stabilizes protein structure	CYLD suppresses CC progression by deubiquitinating Aurora B	(78)
Zhang, 2022	UCHL1	High expression	PROX1	Stabilizes protein structure	UCHL1 promotes CC progression and metastasis by deubiquitinating PROX1	(83)
Lei, 2024	UCHL3	High expression	NRF2	Stabilizes protein structure	UCHL3 promotes CC progression and metastasis by deubiquitinating NRF2	(84)
Bao, 2024	UCHL5	High expression	Wnt/β-catenin	Mediates signal transduction	UCHL5 promotes CC progression by regulating the Wnt/β-catenin signaling pathway	(89)
Li, 2019		Not mentioned	β-catenin	Stabilize protein structure	UCHL5 promotes CC progression by deubiquitinating β-catenin	(90)
Wang, 2017	BAP1	Not mentioned	miR-31	Downstream factor	miR-31 inhibits BAP1 expression and promotes CC progression	(93)
Cao, 2026	CSN5	High expression	ENO3, PKM2, HK2, LDHA	Stabilizes protein structure	CSN5 stabilizes ENO3, increasing glycolytic flux	(98)
Gao, 2015	CSN6	High expression	E6AP	Stabilizes protein structure	CSN6 regulates p53 activity by binding with E6AP, thereby promoting CC progression	(96)
Zhang, 2018	BRCC3	High expression	E-cadherin, Vimentin, MMP-2, MMP-9, Snail-1, Snail-2	Mediates EMT-related signal transduction	BRCC3 promotes CC progression by maintaining a mesenchymal-like phenotype and activating Snail family-mediated EMT signaling, thereby enhancing cell viability, migration and invasion	(99)
Lee, 2016	EIF3F	Low expression	CLU, especially sCLU, AKT, ERK, GSK-3β, Elk-1, Egr-1, p53, p21, Bax	Mediates survival/apoptosis signal transduction	EIF3F suppresses CC progression by interacting with sCLU to interfere with its maturation/secretion, thereby inhibiting AKT/ERK signaling, stabilizing p53, and upregulating p21 and Bax, ultimately inducing apoptosis and inhibiting proliferation and tumor growth	(102)
Wu, 2019	OTUD1	High expression	MCL1	Stabilizes protein structure	OTUD1 promotes CC progression by deubiquitinating MCL1	(108)
Bossler, 2019	OTUD1	Not mentioned	AKT	Mediates signal transduction	OTUD1 inhibits the proliferation of CC cells by inhibiting the level of AKT	(110)

Table I. Continued.

First author, year	DUB	Expression of level in CC	Substrates or related proteins	Role of DUB	Mechanisms and functions	(Refs.)
Xiao, 2024	OTUB2	High expression	FOXM1	Stabilizes protein structure	OTUB2 promotes CC progression by deubiquitinating FOXM1	(113)
Song, 2023	OTUB2	High expression	RBM15, m6A, AKT/mTOR	Downstream factor, mediates signal transduction	RBM15 and m6A are jointly involved in regulating the mRNA level of OTUB2, thereby activating the AKT/mTOR signaling pathway and promoting the malignant behavior of cervical cancer cells	(114)
Yin, 2019	OTUD5	Not mentioned	AKT	Stabilizes protein structure	OTUD5 regulates the sensitivity of CC to radiotherapy by deubiquitinating AKT	(117)

BAP1, BRCA1-associated protein-1; CC, cervical cancer; Cdc25A, cell division cycle 25A; CLU, clusterin; DDB2, DNA damage-binding protein 2; DDR, DNA damage response; DUB, deubiquitinating enzyme; EMT, epithelial-mesenchymal transition; ENO3, enolase 3; FLIPL, FLICE-like inhibitory protein; HDAC, histone deacetylase; HK2, hexokinase 2; HPV, human papillomavirus; KLF6, Krüppel-like factor 6; LDHA, lactate dehydrogenase A; MDC1, mediator of DNA damage checkpoint 1; MDM2, murine double minute protein 2; miR, microRNA; MTDH, metadherin; NRF2, nuclear factor erythroid 2-related factor 2; OTU, ovarian tumor-related protease; PKM2, pyruvate kinase M2; PROX1, prospero homeobox 1; sCLU, secretory CLU; SDS3, HDAC-dependent Sin3A co-repressor complex; UCH, ubiquitin C-terminal hydrolase; USP, ubiquitin-specific protease.

members and to validate their translational utility in the clinical management of CC.

4. JAMM/MPN metallopeptidases: New advances and challenges in CC research

CSN5 (COPS5) and CSN6 (COPS6). As the only metallopeptidase DUBs, members of the JAMM/MPN metallopeptidase family are defined by their Zn^{2+}-dependent catalytic activity (94,95). CSN5 and CSN6 are upregulated in CC, and high CSN5 expression is associated with advanced stage, poor differentiation and lymph node involvement (96,97). Functionally, these proteins promote proliferation, tumor growth, glycolysis and survival while inhibiting apoptosis (96-98). Mechanistically, CSN6 interacts with E6AP and modulates p53 activity, thereby influencing proliferation and apoptosis (96). CSN5 stabilizes enolase 3 (ENO3) by preventing its ubiquitin-dependent degradation, which increases glycolytic flux, and upregulates pyruvate kinase M2, hexokinase 2, lactate dehydrogenase A and lactate production (98). Inhibition of glycolysis with 2-deoxy-D-glucose or ENO3 silencing reverses the oncogenic effects of CSN5 upregulation (98). Together, these findings indicate that JAMM/MPN proteins promote CC progression through coordinated regulation of apoptosis and metabolic reprogramming. The CSN6/E6AP/p53 axis and the CSN5/ENO3 pathway may therefore serve as biomarkers and therapeutic targets.

BRCC3. BRCC3 (also known as BRCC36) is a JAMM/MPN DUB involved in DNA damage signaling, cell cycle control and inflammatory pathways (99). In CC, it acts as an oncogenic regulator; BRCC3 is upregulated in CC tissues, and in HeLa, SiHa and C33A cells compared with in normal cervical controls (99). High expression is associated with advanced FIGO stage, poor differentiation and shorter overall survival, indicating aggressive disease (99). Functionally, BRCC3 promotes cell viability, migration and invasion, whereas its knockdown suppresses these phenotypes *in vitro* (99). Mechanistically, BRCC3 drives EMT. Silencing BRCC3 increases E-cadherin and reduces Vimentin, MMP-2, MMP-9, Snail-1 and Snail-2, indicating loss of a mesenchymal state and reduced invasive capacity (99). These findings support BRCC3 as a prognostic biomarker and potential therapeutic target, particularly for strategies aimed at limiting invasion and metastasis.

EIF3F. EIF3F is a component of the eukaryotic translation initiation factor 3 complex, which also functions as a non-canonical DUB with tumor-suppressive properties (100,101). In CC, EIF3F is markedly downregulated in HeLa and CaSki cells, whereas clusterin (CLU), particularly the secretory form (sCLU), is highly expressed (102). Restoring EIF3F suppresses proliferation, reduces colony formation, induces apoptosis *in vitro* and inhibits tumor growth in xenograft models (102). Mechanistically, EIF3F binds the α-chain of sCLU in the cytoplasm and disrupts its maturation and secretion, reducing intracellular precursor CLU and mature α/β-CLU (102). This inhibition suppresses AKT and ERK signaling, reduces GSK-3β phosphorylation, downregulates EST-like-1 (Elk-1) and early growth response 1 (Egr-1), stabilizes p53 and increases p21 and Bax expression, partly in a p53-independent manner (102).

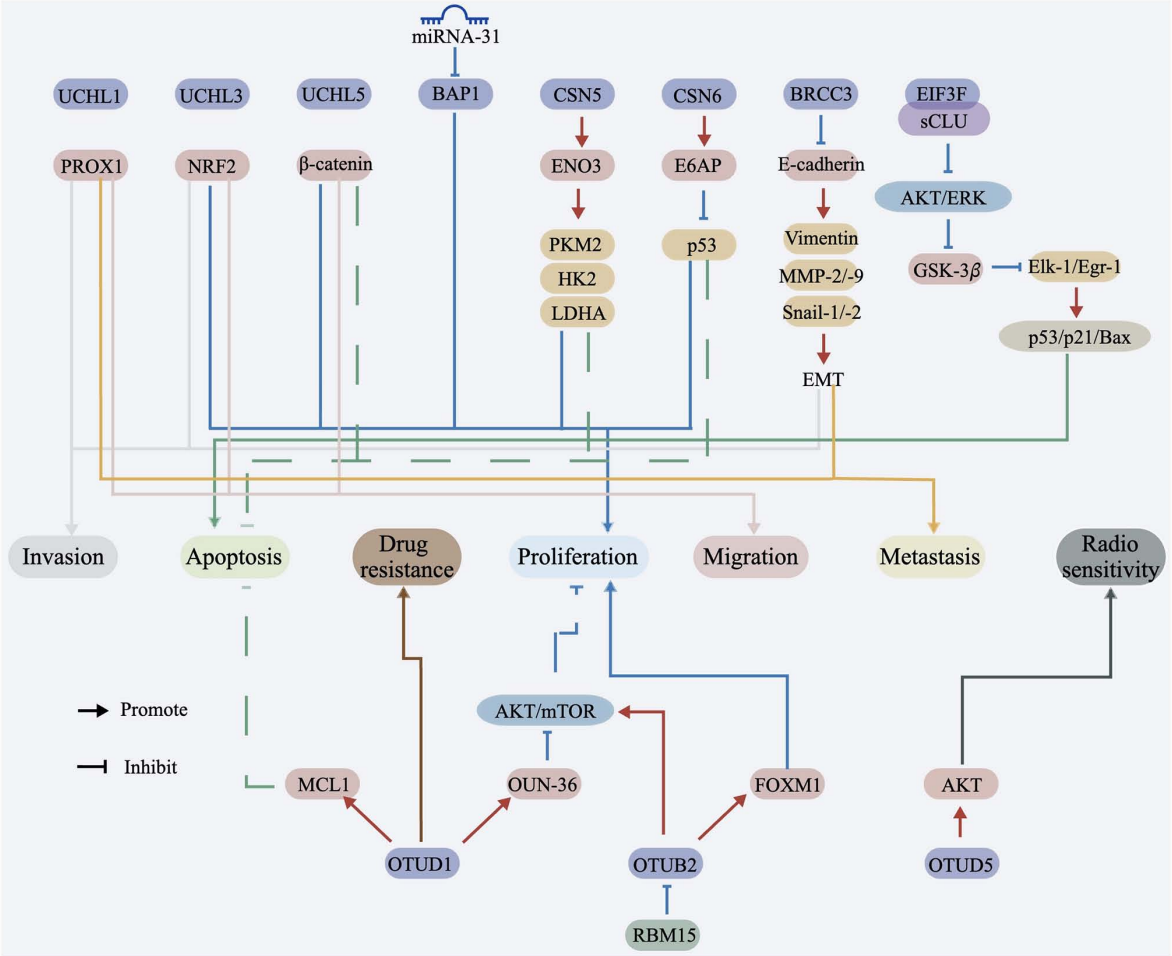

Figure 3. Regulatory roles of DUBs and associated factors in tumor progression. Schematic diagram illustrating how multiple DUBs and related regulatory proteins contribute to malignant phenotypes in CC through distinct downstream signaling pathways. Members of the UCH family, including UCHL1, UCHL3 and UCHL5; as well as BAP1, CSN5, CSN6, BRCC3, EIF3F, OTUD1 and OTUB2, modulate the stability or activity of key effectors involved in tumor progression. Their downstream targets include PROX1, NRF2, β-catenin, ENO3, E6AP, p53, E-cadherin, vimentin, MMP-2/-9, Snail-1/-2, GSK-3β, Elk-1/Egr-1, p53/p21/Bax, MCL1, OUN-36, AKT/mTOR, FOXM1 and RBM15. Through these regulatory interactions, DUBs influence major cancer-related processes, including proliferation, apoptosis, invasion, migration, metastasis and drug resistance. Upstream regulation by miRNA-31 targeting BAP1 is also shown, and pathway crosstalk involving AKT/ERK and AKT/mTOR signaling is highlighted. Arrows indicate activation or positive regulation, whereas lines indicate inhibition or negative regulation. Overall, the diagram emphasizes the central role of deubiquitination-dependent signaling in coordinating tumor growth, dissemination and therapeutic response in CC. BAP1, BRCA1-associated protein-1; CC, cervical cancer; DUB, deubiquitinating enzyme; EMT, epithelial-mesenchymal transition; ENO3, enolase 3; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; miRNA, microRNA; NRF2, nuclear factor erythroid 2-related factor 2; OTU, ovarian tumor-related protease; PKM2, pyruvate kinase M2; PROX1, prospero homeobox 1; UCH, ubiquitin C-terminal hydrolase; USP, ubiquitin-specific protease.

Rescue experiments show that EIF3F silencing restores CLU expression and downstream survival signaling (102). Although prognostic data remain limited, the combined loss of EIF3F and upregulation of CLU suggest that EIF3F deficiency contributes to apoptosis resistance and tumor progression (102). Restoring EIF3F activity or targeting CLU-dependent survival pathways may therefore provide therapeutic strategies.

Collectively, current evidence indicates that JAMM/MPN metallopeptidase family DUBs largely promote tumor progression in CC, although some members, such as EIF3F, act as tumor suppressors in specific contexts. Overall, this family has been implicated in the regulation of CC progression through protein stability, apoptosis, EMT and metabolic reprogramming. Oncogenic members, including CSN5 and BRCC3, enhance tumor growth, survival, glycolysis and invasion through pathways such as CSN5/ENO3-mediated metabolic activation and BRCC3-driven EMT signaling. By contrast, EIF3F suppresses malignant progression by disrupting the anti-apoptotic CLU pathway and restoring pro-death signaling (Fig. 3; Table I). Clinically, dysregulated expression of JAMM/MPN metallopeptidase family members is associated with advanced stage, poor differentiation, metastasis and reduced survival, supporting their potential utility as biomarkers of disease progression. Together, these findings suggest that JAMM/MPN proteins contribute to CC pathogenesis in a context-dependent but mechanistically convergent manner. Targeting oncogenic members while restoring tumor-suppressive ones may represent a promising strategy for CC therapy.

5. OTUs: Association with CC and implications for clinical treatment

OTUs are a vital subset of the DUB family. Initially discovered as genes essential for *Drosophila* egg formation, they share

homology with ovarian cancer genes. This group contains 19 proteases and can be primarily classified into four subfamilies: The Otubain subfamily, the OTUD subfamily, the A20 subfamily and the OTULIN subfamily (103,104).

OTUD1. OTUD1 is a conserved OTUD family DUB involved in cell signaling, protein homeostasis, cell cycle control and immune regulation (103,105,106). Although it generally acts as a tumor suppressor in a number of types of cancer (107), OTUD1 functions in a context-dependent oncogenic role in CC. Bioinformatics analyses have shown that OTUD1 is highly expressed in CC and is associated with poor prognosis (108). Functionally, OTUD1 exerts opposite effects on CC cells through different mechanisms (108). Mechanistically, OTUD1 interacts with MCL1 and enhances its deubiquitination and stability, thereby antagonizing BH3 mimetic-induced apoptosis. Accordingly, OTUD1 knockdown sensitizes CC cells to ABT-263 (Navitoclax; Bcl-2 family protein inhibitor), whereas OTUD1 upregulation increases resistance (108,109). In addition, the OTUD1-derived peptide OUN-36 inhibits AKT signaling by binding the RH domain of AKT and blocking its PIP3-binding site, thereby preventing membrane localization, reducing phosphorylation and suppressing CC cell proliferation (110,111). These findings suggest that OTUD1 may serve as both a prognostic marker and a therapeutic target in CC. The OTUD1/MCL1 axis and OUN-36-mediated AKT inhibition represent promising strategies for drug development.

OTUB2. OTUB2, a member of the OTU DUB family, promotes tumor progression by regulating DNA damage repair, immune escape and metastasis-related signaling pathways (112). In CC, OTUB2 is highly expressed in tissues and cell lines, including CSCC, and its expression is associated with poor prognosis (113,114). Functionally, OTUB2 promotes CC cell proliferation, tumor growth and malignant progression (113,114). Mechanistically, OTUB2 stabilizes FOXM1 through deubiquitination, thereby enhancing proliferation (113). OTUB2 expression is also upregulated by RBM15-mediated m6A modification, and elevated OTUB2 activates the AKT/mTOR signaling pathway to drive malignant phenotypes in CSCC cells (114). Clinically, these findings support OTUB2 as a marker of poor prognosis in CC. The OTUB2/FOXM1 axis and the RBM15/m6A/OTUB2/AKT/mTOR pathway represent potential therapeutic targets.

OTUD5. OTUD5 is a deubiquitinating cysteine protease involved in cell cycle regulation, DNA damage repair and signal transduction, and its dysregulation has been linked to tumor development (115). In CC, OTUD5 is downregulated and associated with poor prognosis (116). Its expression is negatively associated with FIGO stage, lymph node metastasis and tumor type, suggesting a tumor-suppressive role (116). Functionally, OTUD5 inhibits CC progression and increases radiosensitivity (116,117). Mechanistically, bioinformatics analyses have identified regulatory networks involving co-expressed genes, miRNAs and interacting proteins associated with OTUD5 (116). OTUD5 upregulation reduces AKT ubiquitination and enhances radiosensitivity in CC cells, indicating that the OTUD5/AKT axis serves an important role in radiotherapy response (117). These findings indicate that OTUD5 may serve as a prognostic and predictive biomarker for radiotherapy response, as well as a potential therapeutic target in CC (116,117).

In summary, the OTU family serves diverse and context-dependent roles in CC by regulating the stability and activity of key substrates involved in apoptosis, cell cycle control, DDR, signal transduction and therapeutic sensitivity (Fig. 3; Table I). Only a limited number of OTU family members have been investigated in CC, but current evidence indicates that they contribute to tumor progression through both tumor-promoting and tumor-suppressive mechanisms. OTUD1 and OTUB2 generally exert oncogenic effects by stabilizing proteins such as MCL1 and FOXM1, or by activating signaling pathways including AKT and AKT/mTOR, thereby promoting proliferation, survival and treatment resistance. By contrast, OTUD5 may function as a tumor suppressor or radiosensitizer in specific contexts, highlighting the functional heterogeneity of this family. Notably, the biological effects of OTU proteins extend beyond individual enzyme-substrate interactions and instead reflect a broader regulatory network in which multiple members converge on shared pathways, particularly those involved in AKT signaling, cellular survival and stress responses. Clinically, aberrant expression of OTU family members is strongly associated with prognosis, FIGO stage, lymph node metastasis and radiotherapy response, indicating their potential value as biomarkers for disease stratification and treatment prediction. Emerging approaches, including peptide-based interventions, targeted inhibitors and DUBTAC-related strategies, further support their translational potential. A deeper understanding of OTU molecular functions and regulatory interactions may therefore enable improved biomarker development and precision therapy in CC.

6. Crosstalk and pathway convergence of DUBs in CC

Although the roles of individual DUBs in CC have been increasingly characterized, growing evidence suggests that their biological importance extends beyond isolated enzyme-substrate interactions. Instead, multiple DUBs participate in interconnected regulatory networks through shared substrates, overlapping signaling pathways and common biological processes. Therefore, a comprehensive understanding of DUB function in CC requires both substrate-level mapping and network-level analysis of crosstalk.

One notable feature is the convergence of multiple DUBs on proteins involved in cell cycle progression and checkpoint control. For example, both USP3 and USP7 have been reported to stabilize Cdc25A, suggesting that maintenance of Cdc25A is a shared requirement for CC cell proliferation. This observation raises the possibility of redundant, cooperative or context-dependent regulation of the same substrate by distinct DUBs. In addition, regulation of MDM2 by USP14 and p53 by USP19 further supports convergence on the cell cycle checkpoint network. Together, these findings suggest that DUBs collectively promote cell cycle progression by sustaining cell cycle transition and weakening stress-induced checkpoint responses.

Beyond shared substrates, multiple DUBs converge on major oncogenic signaling pathways. FOXM1 emerges as a central node, as USP21, USP39 and OTUB2 enhance

FOXM1-associated oncogenic activity through distinct mechanisms, including protein stabilization, alternative splicing regulation and pathway reinforcement. This suggests that FOXM1 may function as a convergence hub for DUB-mediated regulation in CC, contributing to proliferation, survival and radioresistance. Similarly, the Wnt/β-catenin pathway is regulated by several DUBs. UCHL5/UCH37 stabilize β-catenin, while USP45 enhances Myc stability, a key downstream effector of Wnt signaling. Together, these effects amplify pathway output and promote malignant progression.

A comparable pattern is observed in the PI3K/AKT pathway. USP18 and OTUB2 promote pathway activation, whereas OTUD1 and OTUD5 regulate AKT signaling in a context-dependent manner. This observation suggests that DUBs influence not only protein stability but also signaling dynamics and cellular stress responses. Accordingly, DUB function in CC should not be strictly categorized as oncogenic or tumor-suppressive, but instead interpreted within specific molecular and signaling contexts.

DUB-mediated regulation must also be considered in the context of HPV-driven carcinogenesis, a defining feature of CC. Several DUBs directly modulate viral oncoproteins or their downstream pathways. USP11 and USP15 stabilize HPV-16 E7 and E6, respectively, and CSN6 regulates E6AP-mediated p53 degradation. USP7 further contributes by modulating the DDR, potentially supporting survival of HPV-transformed cells under replication stress. Collectively, these findings support a model in which DUBs function as components of an integrated regulatory network rather than isolated enzymes. A deeper understanding of DUB crosstalk and pathway convergence will be essential for identifying key regulatory nodes and developing effective DUB-targeted therapies in CC.

7. DUB-based therapeutic strategies for CC

Small-molecule DUB inhibitors: Current progress and translational challenges. Despite strong biological rationale for targeting DUBs, the clinical translation of DUB inhibitors remains in its early stages. Most DUB-targeting compounds are still confined to preclinical development, including inhibitors of PSMD14, UCHL1, USP1, USP2, USP4, USP7, USP8, USP9X, USP10/USP13, USP11, USP14, USP20 and USP30 (118). These agents have shown promising antitumor, anti-inflammatory or neuroprotective effects in biochemical assays, cell-based systems and animal models, supporting the druggability of multiple DUB family members; however, most have not progressed beyond preclinical proof-of-concept. VLX1570, a dual inhibitor of UCHL5 and USP14, is one of the few to have entered early-phase clinical trials in oncology (118). However, its development was later suspended owing to safety concerns, highlighting key translational challenges in this field. Future work should therefore extend beyond mechanistic validation in CC models, and prioritize the development of inhibitors with improved selectivity, safety and pharmacokinetic properties. In addition, rational patient stratification and biomarker-guided approaches will be essential to support successful translation into phase I/II clinical trials.

DUBTACs: An emerging strategy for targeted protein stabilization in CC. DUBTACs represent an emerging strategy for targeted protein stabilization. In contrast to proteolysis-targeting chimeras (PROTACs), which induce degradation of target proteins through recruitment of E3 ubiquitin ligases, DUBTACs recruit DUBs to remove degradation-associated ubiquitin chains from proteins of interest, thereby preventing proteasomal degradation and increasing protein stability (119). A typical DUBTAC consists of three components: A ligand for the target protein, a ligand for the recruited DUB and a chemical linker (120). DUBTACs induce ternary complex formation by bringing the target protein and a DUB into close proximity; this process facilitates the cleavage of K48-linked polyubiquitin chains, extending the half-life of the target protein (121). This approach offers a strategy to stabilize proteins that are beneficial for disease control but difficult to modulate using conventional small-molecule activators or inhibitors.

The feasibility of this approach, although still at an early stage of development, has been demonstrated in several studies. Early work has shown that OTUB1 can be chemically recruited to stabilize otherwise unstable proteins, establishing proof of concept for pharmacological redirection of DUB activity (122). This strategy has been expanded to transcription factors and other traditionally 'undruggable' proteins in subsequent studies, suggesting the broad application potential of DUBTACs (123). Specifically, a well-established study (123) has developed three series of transcription factor-targeting DUBTACs (TF-DUBTACs), namely FOXO-DUBTAC, p53-DUBTAC and interferon regulatory factor (IRF)-DUBTAC (123). These TF-DUBTACs selectively stabilize the tumor suppressor transcription factors FOXO3A, p53 and IRF3 in cells, respectively, in an OTUB1-dependent manner (123). Recently, USP7-based DUBTACs have been reported to stabilize AMPK and activate AMPK signaling in HeLa cells, providing direct evidence that this strategy can function in a CC-derived cellular context and produce measurable downstream biological effects (124). These findings indicate that DUBTAC technology is not only conceptually attractive but also experimentally feasible. However, compared with PROTACs and other targeted protein regulation technologies, DUBTACs remain less developed, with limited available DUB recruiters, an incomplete understanding of ternary complex formation and no clinical-stage agents reported to date (119).

In CC, DUBTACs may offer several potential applications. First, they may stabilize tumor suppressors or negative regulators of oncogenic pathways. For example, p53 is often functionally impaired in CC because of HPV E6/E6AP-mediated, ubiquitin-dependent degradation, which suggests that restoring p53 stability helps recover its cell cycle arrest and pro-apoptotic functions (125). Similarly, KLF6 (15) and CYLD (78) are potential candidates, as both exhibit tumor-suppressive effects in CC. Second, DUBTACs may enhance radiosensitivity. The USP53/DDB2 and OTUD5/AKT axes regulate the radiation response in CC; thus, stabilization of radiosensitizing proteins serves to improve the susceptibility of tumor cells to radiation-induced DNA damage (75,117). Third, DUBTACs may also be useful for modulating oncogenic and immune-related signaling. Pathways such as FOXM1 (113), AKT/mTOR (126), NF-κB (127) and Wnt/β-catenin (128) are frequently dysregulated in CC, and some DUBs, including USP7 (129) and CYLD (130), are involved in PD-L1 expression and tumor immune regulation.

Despite these prospects, several limitations should be noted. Some recruitable DUBs, such as USP7, also have oncogenic roles in CC, raising the risk of stabilizing oncogenic substrates. The effects of protein stabilization may be context dependent, particularly for DNA repair-related proteins (31,75). In addition, DUBTACs face pharmacological challenges, including large molecular size, poor cell permeability and limited CC-specific preclinical validation (131).

In summary, DUBTAC technology offers a novel strategy for targeted protein stabilization and expands the therapeutic scope of ubiquitin-related interventions in CC. It may be particularly promising for restoring tumor suppressors, enhancing radiosensitivity and stabilizing key negative regulators of oncogenic pathways. However, DUBTACs remain at an early stage of development, with challenges in recruiter selection, target prioritization, ternary complex optimization and safety evaluation. Future studies integrating chemoproteomics, structural biology and functional screening in CC models will be essential to identify suitable substrates and DUB recruiters, and to advance DUBTAC-based precision therapies for CC.

8. Conclusions and future prospects

In conclusion, current evidence indicates that DUBs are biologically important and potentially actionable regulators in CC, although the depth and maturity of available evidence vary substantially among individual family members. Therefore, future research should focus less on simply expanding the list of CC-associated DUBs, and more on prioritizing those with the strongest clinical and translational potential.

Among the DUBs reviewed, USP7 appears to be the most promising near-term candidate because it is supported by relatively consistent evidence linking dysregulated expression, clinicopathological relevance, functional importance and therapeutic tractability. USP8 has also emerged as a strong candidate based on its prognostic associations and *in vivo* functional validation. In addition, USP21, USP53 and OTUD5 warrant particular attention in the context of radiotherapy, where DUB-based patient stratification and radiosensitization strategies may offer practical clinical benefits.

From a therapeutic perspective, small molecule inhibition of oncogenic DUBs currently represents the most feasible route for clinical translation in CC. By contrast, DUBTAC-based approaches remain highly promising but are still at an early developmental stage and will require substantial optimization before clinical application in CC becomes realistic.

Subsequent research should prioritize three key directions: i) Validation of leading DUB candidates in clinically annotated patient cohorts; ii) evaluation in treatment-oriented preclinical models; and iii) biomarker-guided development of DUB-targeted strategies. Ultimately, the greatest near-term progress is likely to come from concentrated work on a limited number of well-supported DUBs rather than from broad but superficial expansion of candidate lists.

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Authors' contributions

CZP collected literature and drafted the manuscript. XXS helped to draft and modify the manuscript. HX conceived the topic of the present review and revised the manuscript. KHB offered significant guidance and critically reviewed this manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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