The role of deubiquitinating enzymes and their inhibitors in esophageal carcinoma (Review)

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Abstract. Esophageal squamous cell carcinoma (ESCC) is a significantly fatal gastrointestinal malignancy worldwide, with complex proteomic remodeling during its onset and progression. Despite advancements in existing multimodal therapy regimens, the prognosis for advanced patients remains inadequate, necessitating the urgent identification of novel therapeutic targets. The Ubiquitin-proteasome system is the principal regulatory mechanism for intracellular protein homeostasis, with deubiquitinating enzymes (DUBs) serving as crucial 'editors' that reverse ubiquitination modifications, significantly influencing the stability, localization and functional regulation of oncoproteins. This review aims to systematically delineate the complex regulatory network of DUBs in ESCC, comprehensively investigate their specific mechanisms within critical oncogenic signaling pathways, including TGF-β, Wnt/β-catenin, NF-κB and Hippo, as well as their roles in epithelial-mesenchymal transition, epigenetic remodeling and the regulation of the immune microenvironment. Furthermore, this review provides a novel cross-cancer perspective by comparing the similarities and differences of DUBs in ESCC and uterine corpus endometrial carcinoma to determine the conserved and tissue-specific functions of ubiquitin-specific protease (USP)14, USP7 and BRCA1-associated protein 1. Furthermore, the preclinical research progress of small molecule inhibitors and proteolysis-targeting chimeras targeting DUBs was also assessed to identify the theoretical basis and translational pathway for the development of next-generation precision oncology therapies.

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Abbreviations: ATP, adenosine triphosphate; ANXA2, annexin A2; BAP1, BRCA1-associated protein 1; CAFs, cancer-associated fibroblasts; CSN5, COP9 signalosome subunit 5; CYLD, cylindromatosis, lysine 63 deubiquitinase; DNMT1, DNA methyltransferase 1; DUBs, deubiquitinating enzymes; DUBTAC, deubiquitinase-targeting chimera; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; EAC, esophageal adenocarcinoma; EC, Esophageal Carcinoma; EC50, half maximal effective concentration; EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; EZH2, enhancer of zeste homolog 2; FOXP4-AS1, FOXP4 antisense RNA 1; G3BP1, Ras-GTPase-activating protein SH3-domain-binding protein 1; GEO, gene expression omnibus; GPX4, glutathione peroxidase 4; H2Aub1, histone H2A monoubiquitination; HIF-1α, hypoxia-inducible factor 1α; IC50, half maximal inhibitory concentration; ICIs, immune checkpoint inhibitors; IKK, inhibitor of κB kinase; JAMM, Jab1/Mov34/Mpr1; JMJD3, Jumonji domain containing 3; LATS, large tumor suppressor; lncRNA, long non-coding RNA; MINDY, MIU-containing novel DUB family proteases; MJD, Machado-Joseph disease protein domain protease; MOF, males absent on the first; NCG, NOD-Prkdcem26Il2rgem26/Gpt; NF-κB, nuclear factor-κB; NOXA, PMAIP1 (phorbol-12-myristate-13-acetate-induced protein 1)/NOXA; NSG, NOD scid gamma; OS, overall survival; OTUs, ovarian tumor proteases; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDX, patient-derived xenograft; Pol ι, DNA polymerase iota; PROTAC, proteolysis targeting chimera; PSMD14, proteasome 26S subunit, non-ATPase 14; PTM, post-translational modification; SAGA, Spt-Ada-Gcn5 acetyltransferase; SMAD, mothers against decapentaplegic homolog; TAZ, transcriptional coactivator with PDZ-binding motif; TCGA, The Cancer Genome Atlas; TGF-β, transforming growth factor-β; TME, tumor microenvironment; UCHs, ubiquitin C-terminal hydrolases; USPs, ubiquitin-specific proteases; WISP1, Wnt-induced signaling protein 1; Wnt pathway, Wnt Signaling Pathway; YAP1, Yes-associated protein 1; ZEB1, zinc finger E-box binding homeobox 1

Key words: esophageal carcinoma, deubiquitinase, biomarkers, tumor occurrence, pathogenesis, diagnosis

6. Pan-cancer mechanism comparison: Esophageal vs. endometrial cancer
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1. Introduction

Esophageal cancer (EC) ranks as the 11th most frequently diagnosed malignancy and the 7th principal cause of cancer-related mortality worldwide, with ~511,000 new cases and 445,000 fatalities recorded in 2022 (1). Furthermore, esophageal squamous cell carcinoma (ESCC) is the predominant pathological type of EC, accounting for >90% of cases (2). It has been characterized by accelerated tumor proliferation and elevated rates of metastasis and recurrence, resulting in an unfavorable prognosis for patients. The advancement of therapeutic techniques, including minimally invasive surgery, targeted therapy and immunotherapy, has improved the 5-year survival rate of patients with ESCC; however, it remains unsatisfactory (3,4). For certain patients with EC, the lesions' location or the disease's advanced stage may make surgery inappropriate, posing specific therapeutic challenges. Chemotherapy and targeted therapies can partially manage EC; however, certain individuals may exhibit drug resistance, resulting in diminished therapeutic effectiveness. For patients with advanced EC, current therapies demonstrate limited effectiveness, requiring the exploration of new potent therapeutic options. Therefore, comprehensive studies on EC occurrence and pathophysiology, as well as the identification of prognostic biomarkers, may yield more accurate recommendations for personalized treatment, enhancing patient prognosis, therapeutic efficacy and quality of life.

Protein ubiquitination is a dynamic and reversible post-translational modification (PTM) involving the covalent attachment of one or more ubiquitin (Ub) proteins, each comprising 76 amino acids, to a substrate protein. This alteration affects various cellular proteins and is involved in various cellular processes (5). In humans, four distinct genes encode Ub, of which Ub A-52 residue ribosomal protein fusion product 1 (UBA52) and ribosomal protein S27a (UBA80) encode a solitary Ub fused at their C-termini to ribosomal proteins L40 and S27a, respectively. The Ub B and Ub C genes are polyubiquitin precursors that occur as tandem repeats (6). Ubiquitination is a cascade reaction comprising three enzymes: Ub-activating enzymes (E1s), Ub-conjugating enzymes (E2s) and Ub ligases (E3s) (7). Furthermore, Ub is activated by E1 in an ATP-dependent manner; it establishes a thioester bond between the active site cysteine of E1 and the C-terminal carboxyl group of Ub. Then, Ub is transferred to E2 through a transthiolation process, covalently bound to the amino group of a lysine residue on the substrate protein by an E3 Ub ligase (8). The following four E3 subtypes have been identified: Homologous to E6-associated protein C-terminus (HECT) type, Really Interesting New Gene (RING) type, U-box type and RING-in-between-RING (RBR) type. RING-type and U-box type E3 ligases directly promote the transfer of Ub from E2 to the substrate protein. HECT-type and RBR-type E3 ligases establish a thioester bond between the cysteine in their active site and Ub before transferring it to the substrate protein (9,10).

Deubiquitinating enzymes (DUBs) are isopeptidases that can cleave either a single Ub or an entire Ub chain from a target protein, thus opposing protein ubiquitination, a crucial PTM that modulates protein stability, activity, subcellular localization and interactions (11,12). DUBs not only reverse ubiquitination but also govern various physiological pathways, such as protein trafficking, chromatin remodeling and cell cycle regulation. Therefore, they are implicated in various clinical disorders (13). Therefore, DUBs have become a research hotspot as therapeutic targets, prompting the establishment of DUB inhibitors, some of which are currently in preclinical development or clinical trials (14). To date, ~100 DUBs have been identified in and are categorized into 9 families: Ub-specific proteases (USPs), ovarian tumor proteases (OTUs), Ub C-terminal hydrolases (UCHs), Machado-Joseph disease protein domain proteases (MJDs, also referred to as Josephins), JAMM/MPN domain-associated zinc-dependent metalloproteases (JAMMs, also known as MPN+), motif interacting with Ub-containing novel DUB family, monocyte chemotactic protein-induced proteins, permuted papain fold peptidases of double-stranded RNA viruses and eukaryotes and zinc finger-containing Ub peptidase 1 (15), with a primary focus on the seven major families that include USPs (Fig. 1). Several studies suggest that DUB dysfunction is markedly associated with the onset and progression of EC (16-18). They may function as oncogenes, enhancing critical proteins associated with proliferation, metastasis and drug resistance [e.g., β-catenin, Snail, Yes-associated protein (YAP)1, programmed death-ligand 1 (PD-L1)], or they may serve as tumor suppressor genes [e.g., BRCA1-associated protein 1 (BAP1), cylindromatosis, lysine 63 deubiquitinase (CYLD)], wherein their deletion or mutation may result in the inhibition of tumor-suppressive functions (16,17,19-62) (Table I).

This review aims to systematically elucidate the complex regulatory network of DUBs in EC. This study will go beyond single-molecule descriptions to classify and analyze DUBs based on signaling pathways (TGF-β, Wnt, NF-κB, Hippo) and summarize essential biological processes [epithelial-mesenchymal transition (EMT), epigenetics, immune regulation], while assessing their viability as therapeutic targets by integrating preclinical quantitative data.

2. Methodology and literature search strategy

This study followed a Narrative Review methodological framework to conduct extensive and comprehensive qualitative and quantitative analysis of existing literature and fill the gaps in the systematic understanding of DUBs in EC.

Literature identification and search strategy. The literature search was primarily based on the following key databases to ensure data comprehensiveness and rapid availability: PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Embase (https://www.embase.com/) and Google Scholar (https://

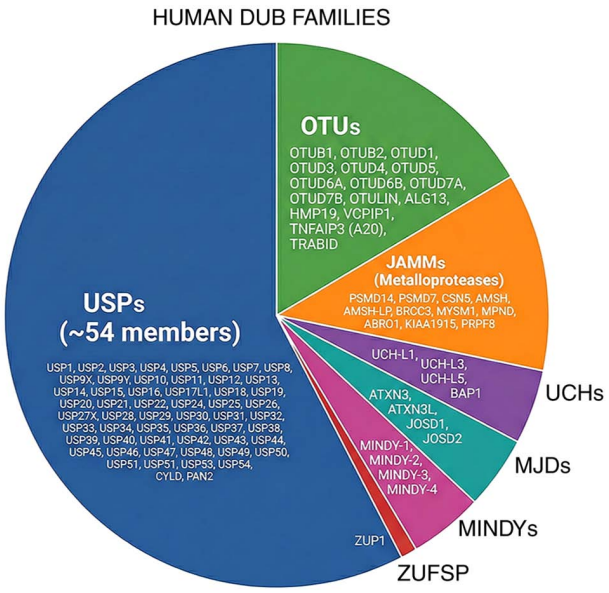

Figure 1. Genomic landscape and structural classification of the human DUB superfamily. This schematic illustrates the systematic classification and structural diversity of the human DUB superfamily. The human genome encodes approximately 100 DUBs, which are categorized into seven evolutionarily conserved families based on their catalytic domain architecture. The USP family represents the largest cohort, comprising approximately 54 members (e.g., USP1-USP54, CYLD). Other specialized families include the OTU family, the JAMM family (the sole class of metalloproteases, including PSMD14 and CSN5) and the UCH, MJD, MINDY and ZUFSP families. This hierarchical organization underscores the diverse structural foundations that govern DUB functional specificity. DUB, deubiquitinating enzyme; USP, ubiquitin-specific protease; CYLD, cylindromatosis, lysine 63 deubiquitinase; OTU, ovarian tumor; JAMM, Jab1/Mov34/Mpr1; PSMD14, proteasome 26S subunit, non-ATPase 14; CSN5, COP9 signalosome subunit 5; UCH, ubiquitin C-terminal hydrolase; MJD, Machado-Joseph disease protein domain protease; MINDY, MIU-containing novel DUB family proteases.

scholar.google.com/). Furthermore, ClinicalTrials.gov was referenced to acquire data on the ongoing clinical trials. In addition, bioinformatics analysis data were obtained from The Cancer Genome Atlas (TCGA) (https://www.cancer.gov/ccg/) and Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/) databases to supplement transcriptome-level evidence. i) Search timeline: Studies from 1st January 2000 to February 2025, specifically high-quality studies published in the last 5 years (2020-2025), were analyzed, reflecting the latest advances in the field. ii) Search keywords: Boolean logic combinations were employed, mainly including: iii) Disease-related: 'Esophageal cancer', 'esophageal squamous cell carcinoma' and 'esophageal adenocarcinoma'. iv) Target-related: 'Deubiquitinating enzymes', 'DUBs', 'ubiquitin-specific proteases' (USPs), 'UCH', 'OTU', 'BAP1', proteasome 26S subunit, non-ATPase 14 ('PSMD14') and specific family/member names. v) Mechanism and function: 'Signaling pathway', 'EMT', 'drug resistance', 'metastasis', 'prognosis' and 'immunotherapy'.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Studies with research subjects specifically identified as having EC [including ESCC and esophageal adenocarcinoma] cell lines, animal models or clinical tissue specimens; ii) original studies and reviews addressing differential expression, molecular mechanisms, prognostic significance or small-molecule inhibitors of DUBs; iii) studies indicating key quantitative data (e.g., IC_{50} values, hazard ratios, P-values, tumor volume inhibition rates) were prioritized to meet the report's requirements for quantitative details; and iv) studies on DUB mechanisms in endometrial cancer were selected for lateral comparative analysis. The following exclusion criteria were applied: i) Studies only focusing on E3 Ub ligases and lacking DUB data; ii) bioinformatics prediction articles lacking biological experimental validation (unless independently validated in clinical cohorts); iii) Non-English or non-Chinese studies; and iv) conference abstracts with incomplete text or data.

3. Reconstructing the regulatory network of DUBs through mechanisms and signaling pathways

The DUBs in EC cells do not function in isolation; instead, they constitute a complex signal transduction network by carefully regulating the stability of essential proteins in critical signaling pathways. This section will categorize important oncogenic signaling pathways to comprehensively investigate the specific mechanisms and functional implications of DUBs within these pathways (Fig. 2).

TGF-β signaling pathway: DUB-mediated signal amplification and metastasis driving. The transforming growth factor-β (TGF-β) signaling pathway has a 'double-edged sword' function in tumor biology: It suppresses cell proliferation in initial stages while facilitating tumor invasion and metastasis via EMT in later stages. In EC, DUBs play a crucial role in all phases of this signal transduction, from receptor stability to the activity of downstream effector SMADs (63).

Receptor-level regulation. It has been observed that UCH37 (UCHL5) can interact with the inhibitory SMAD7 and be recruited to the type I TGF-β receptor (TGFBR1). UCH37 inhibits receptor degradation facilitated by the E3 ligase SMURF by deubiquitinating TGFBR1, thus maintaining the receptor and promoting TGF-β signaling (64). In EC, this pathway may result in the persistent stimulation of TGF-β signaling, thus enhancing cellular migration and invasion abilities.

The USP4, USP11 and USP15 cluster of USPs has been reported to function either in complexes or independently, augmenting TGF-β signaling through the deubiquitination of the type I receptor; this modulation is directly associated with initiation of EMT processes and enhanced metastatic potential (65).

Regulation of effector SMADs. USP9X, as a principal positive regulator of the TGF-β pathway, can deubiquitinate SMAD4. SMAD4 is the principal mediator of TGF-β signaling and primarily translocates the SMAD2/3 complex into the nucleus. USP9X inhibits the nuclear export and subsequent degradation of SMAD4 by removing monoubiquitination modification, thus preserving the nuclear stability of the SMAD complex and facilitating the transcription of TGF-β downstream target genes, including Snail and Slug. Furthermore, upregulated USP9X expression in EC has been demonstrated to substantially correlate with adverse prognosis and chemotherapy resistance (40).

Table I. Overview of DUBs involved in esophageal cancer, their targets, cancer types and functional outcomes.

DUB family	Specific DUB	Major targets (substrates)	Pathways/mechanisms involved	Cancer type	Biological function/prognostic relevance	(Refs.)
USPs	USP7	p53, MDM2, HIF-1α, PD-L1, EZH2	Wnt, P53, epigenetics, immunity	ESCC, EAC	Oncogenic; stabilizing HIF-1α leads to hypoxia adaptation; stabilizing PD-L1 leads to immune evasion; high expression means poor prognosis	(19-23)
	USP14	YAP1, IκB-α, CXCR4	Hippo, NF-κB, proteasome	ESCC	Oncogenic; enhances radioresistance; promotes recurrence; poor prognostic indicator	(17,24-29)
	USP10	MOF, ANLN, p53, PD-L1	Wnt, cell cycle, immunity	ESCC	Dual role (mainly oncogenic): Activates Wnt via MOF; stabilizes PD-L1 via FOXP4-AS1	(30-35)
	USP21	G3BP1, MOF	Wnt/β-catenin, STAT3	ESCC	Oncogenic; promotes glycolysis and metastasis	(36-38)
	USP18	ZEB1	EMT	ESCC	Oncogenic; promotes invasion and metastasis	(39)
	USP9X	SMAD4, YAP, Survivin	TGF-β, Hippo	ESCC	Oncogenic; high expression correlates with chemoresistance and poor survival	(40-42)
	USP53	Axin1	Wnt/β-catenin	ESCC	Tumor suppressor; low expression causes Axin1 degradation, activating Wnt	(43-45)
OTUs	OTUB1	Snail	EMT	ESCC	Oncogenic; promotes metastasis; regulated by miR-542-3p	(16,46,47)
	OTUB2	YAP1/TAZ	Hippo	ESCC	Oncogenic; maintains stemness and glycolysis	(48,49)
UCHs	UCHL1	(Promoter Methylation)	Epigenetics	ESCC	Tumor suppressor (often inactivated by promoter methylation); methylation is an independent prognostic factor	(50-52)
	BAP1	KLF5	Cell cycle, DNA repair	ESCC	Tumor suppressor (often mutated); mutations correlate with poor prognosis	(53-57)
	UCH37	TGFBR1	TGF-β	ESCC	Oncogenic; enhances TGF-β signaling	(24,58)
JAMMs	PSMD14	Snail	EMT	ESCC	Oncogenic; initiates EMT; high expression predicts short survival	(59,60)
MJDs	JOSD2	CTGF	Proliferation	ESCC	Oncogenic; enhances proliferation and drug resistance	(61)
Others	CYLD	TRAF2/6, NEMO	NF-κB	ESCC	Tumor suppressor; inhibits NF-κB; low expression promotes stemness	(62)

DUB, deubiquitinating enzyme; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; USPs, ubiquitin-specific proteases; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1; p53, tumor protein p53; MDM2, mouse double minute 2 homolog; HIF-1α, hypoxia-inducible factor 1α; PD-L1, programmed death-ligand 1; EZH2, enhancer of zeste homolog 2; YAP1,Yes-associated protein 1; IκB-α, nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α; CXCR4, C-X-C chemokine receptor type 4; MOF, males absent on the first; ANLN, anillin actin binding protein; FOXP4-AS1, FOXP4 antisense RNA 1; STAT3, signal transducer and activator of transcription 3; SMAD4, mothers against decapentaplegic homolog 4; Survivin, baculoviral IAP repeat containing 5; Snail, Snail family transcriptional repressor 1; ZEB1, Zinc finger E-box binding homeobox 1.

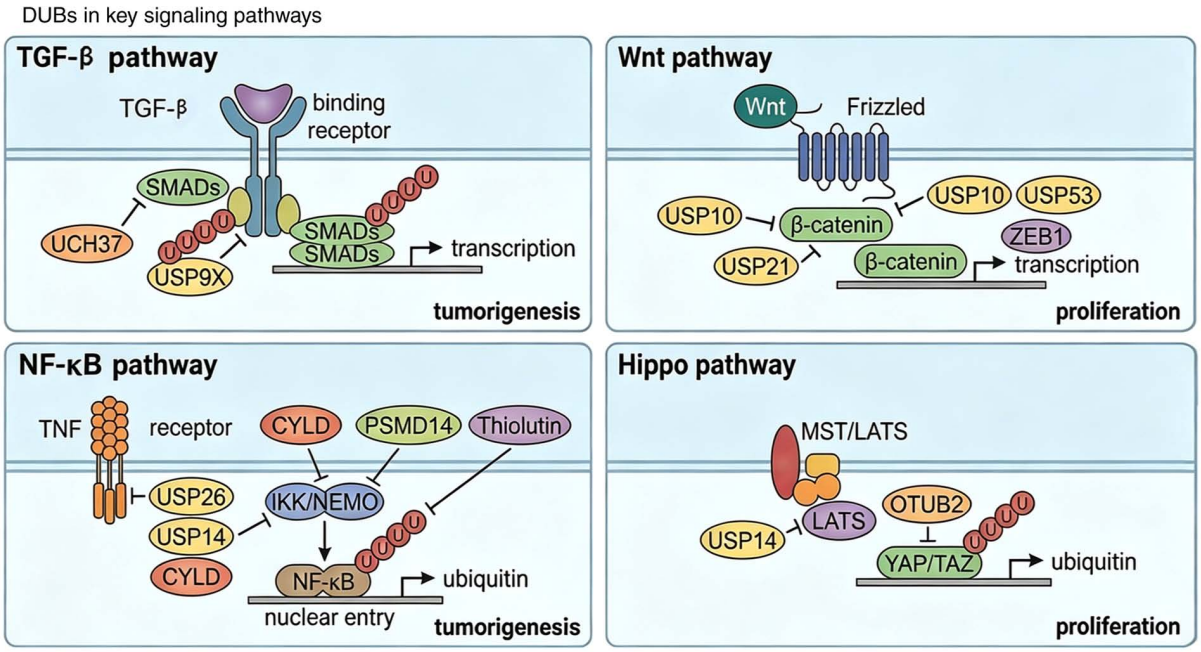

Figure 2. DUB-mediated regulatory networks in oncogenic signaling cascades. This figure delineates the precise roles of specific DUBs in modulating protein homeostasis within key signaling pathways that drive tumorigenesis and cell proliferation. TGF-β pathway: UCH37 and USP9X enhance transforming growth factor-induced oncogenesis by deubiquitinating and stabilizing SMAD proteins. Wnt pathway: USP10, USP21 and USP53 regulate the stability and nuclear transcriptional activity of β-catenin, thereby promoting cellular proliferation. NF-κB pathway: A complex regulatory circuit is shown where CYLD functions as a negative regulator, while PSMD14 facilitates NF-κB nuclear entry by stabilizing the IKK/NEMO complex. Thiolutin is highlighted as a potent small-molecule inhibitor of this axis. Hippo pathway: USP14 and OTUB2 antagonize the degradation of LATS and YAP/TAZ, respectively, thereby bypassing tumor-suppressive constraints to accelerate cell growth. DUB, deubiquitinating enzyme; TGF-β, transforming growth factor-β; USP, ubiquitin-specific protease; UCH, ubiquitin C-terminal hydrolase; SMAD, mothers against decapentaplegic homolog; Wnt pathway, Wnt signaling pathway; NF-κB, nuclear factor-κB; CYLD, cylindromatosis, lysine 63 deubiquitinase; PSMD14, proteasome 26S subunit, non-ATPase 14; IKK, inhibitor of κB kinase; LATS, large tumor suppressor; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif.

In the advanced stages of EC, the TGF-β pathway predominantly demonstrates oncogenic characteristics. The aforementioned DUBs (UCH37, USP9X) function primarily as amplifiers of TGF-β pro-metastatic signals by stabilizing receptors or critical transcription factors. In contrast to normal tissues, the excessively elevated expression of these DUBs in tumor tissues disrupts the self-regulatory mechanisms of TGF-β signaling (including SMURF-mediated negative feedback), resulting in the irreversible onset of EMT. Thus, inhibiting these DUBs could selectively obstruct the carcinogenic pathway of TGF-β while maintaining its homeostatic roles.

Wnt/β-catenin signaling pathway: Stemness maintenance and epigenetic crosstalk. The aberrant activation of the Wnt/β-catenin signaling pathway is the primary driver of stemness, cell proliferation and chemoresistance in ESCC. Furthermore, it has been observed that DUBs elevate β-catenin levels directly or indirectly via different mechanisms that bypass its degradation complex.

USP10 and the epigenetic-Wnt axis. In ESCC, USP10 does not directly deubiquitinate β-catenin; rather, it stabilizes the histone acetyltransferase lysine acetyltransferase 8, also known as males absent on the first (MOF). Research indicates that USP10 deubiquitinates MOF, resulting in increased quantities of MOF protein. The stabilized MOF subsequently accumulates at the promoter region of the annexin A2 (ANXA2) gene, enhancing ANXA2 transcription by increasing H4K16ac (acetylation of histone H4 at lysine 16) modifications. ANXA2 is an established activator of Wnt signaling. The 'USP10-MOF-ANXA2-Wnt' axis indirectly yet significantly promotes the Wnt/β-catenin pathway, facilitating the malignant progression of ESCC (30). This demonstrates the complexity of deubiquitinating enzymes regulating classical signaling pathways via epigenetic processes.

Direct regulation of canonical pathways. USP21 stabilizes Ras-GTPase-activating protein SH3-domain-binding protein 1 (G3BP1) by deubiquitination. G3BP1 accumulation can suppress the β-catenin degradation complex, thus activating Wnt signaling and facilitating cell growth (36).

USP13 stabilizes Wnt-induced signaling protein 1 (WISP1), forming a positive feedback loop to stimulate the Wnt/CTNNB1 pathway, a mechanism that promotes tumor growth and also mediates immune evasion (66).

Tumor suppressive role of USP53. In contrast to the aforementioned oncogenic DUBs, USP53 demonstrates tumor-suppressive characteristics in endometrial carcinoma. The inhibition of USP53 prevents the deubiquitination of Axin1, a crucial negative regulator of the Wnt pathway and a scaffold protein within the degradation complex, resulting in the proteasomal degradation of Axin1. The absence of Axin1 permits β-catenin to evade degradation, translocate to the nucleus and aberrantly activate Wnt signaling (43).

DUBs in the Wnt pathway demonstrate functional diversity. Although the majority (USP10, USP21, USP13)

have oncogenic properties, USP53 indicates that the effect of DUBs on the same pathway is contingent upon whether their substrate functions as an activator or a repressor. This indicates that the development of DUB inhibitors targeting the Wnt pathway necessitates significant selectivity to prevent the inadvertent inhibition of tumor suppressors such as USP53, which may be counterproductive.

NF-κB signaling pathway and the inflammatory microenvironment. The NF-κB pathway bridges chronic inflammation and EC advancement, serving as an essential mechanism that mediates chemotherapy resistance, particularly to platinum-based drugs.

Loss of CYLD negative regulation. CYLD is a member of the USP family and a classical negative regulator of NF-κB. It specifically removes K63-linked Ub chains from TNF receptor associated factor 2 (TRAF2), TRAF6 and inhibitor of NF-κB kinase (IKK) regulatory subunit gamma (NEMO), obstructing IKK complex activation. In ESCC, CYLD is frequently downregulated due to genetic alterations or post-transcriptional regulation. For instance, microRNA (miR)-181b, which is abundantly expressed in EC stem cells, directly targets and inhibits CYLD, alleviating the repression on NF-κB and establishing a STAT3/miR-181b/CYLD positive feedback loop that promotes inflammation-related carcinogenesis and the maintenance of stemness (62). The absence of CYLD has also been found to promote tumor angiogenesis (67).

USP14 and NF-κB activation. In contrast to CYLD, USP14 is typically regarded as a positive regulator of NF-κB. Although the precise substrates of USP14 in EC remain incompletely understood, in related models, USP14 promotes prolonged NF-κB activation via deubiquitinating the upstream kinases of IκB-α or by directly influencing the degradation kinetics of IκB-α. Furthermore, enhanced USP14 expression correlates with NF-κB-mediated tumor advancement in esophageal and endometrial cancers (68).

Hippo-YAP1/transcriptional coactivator with PDZ-binding motif (TAZ) signaling pathway: Mechanical stress and chemoresistance. The Hippo pathway is the principal regulator of organ size, contact inhibition and carcinogenesis, with YAP1 and TAZ serving as its primary transcriptional co-activators.

USP14-mediated radioresistance. USP14 is significantly increased in EC tissues, particularly in radioresistant cell lines. Mechanistic studies demonstrate that USP14 directly associates with YAP1, destroying its K48-linked Ub chains and inhibiting its proteasomal degradation. The activation of the USP14-YAP1 axis significantly increases radiation resistance and the proliferative potential of EC cells (17).

Metabolic reprogramming by OTU deubiquitinase, Ub aldehyde binding 2 (OTUB2). OTUB2 is a member of the OTU family and has been observed to promote the stemness, glycolytic metabolism and invasive ability of tumor cells in ESCC by directly deubiquitinating and stabilizing YAP1 and TAZ (48).

USP36 and nucleolar stress. USP36 has been recognized as a deubiquitinase for YAP, facilitating the malignant development of ESCC by stabilizing YAP (69).

DUBs in epigenetic regulation. The DUBs regulate cytosolic signaling proteins and also penetrate the nucleus to alter the chromatin landscape by influencing histone-modifying enzymes or directly modifying histones.

USP7 and enhancer of zeste homolog 2 (EZH2)/Jumonji domain containing 3 (JMJD3). USP7 is a key node in epigenetic modulation. It stabilizes the histone demethylase JMJD3 to enhance EC cell proliferation and interacts with EZH2, the catalytic subunit of polycomb repressive complex 2 (19). USP7 deubiquitinates EZH2, maintaining its elevated expression levels, which in turn silences tumor suppressor genes through H3K27me3 modification. The levels of the USP7/EZH2 complex are positively associated with tumor grade and adverse prognosis (70).

USP22 and the Spt-Ada-Gcn5 acetyltransferase (SAGA) complex. USP22, an essential member of the deubiquitination module of the SAGA transcriptional coactivator complex, is responsible for the removal of monoubiquitination from histones H2A and H2B (H2Aub1/H2Bub1). This modification is generally associated with transcriptional activity. In EC, elevated USP22 expression is substantially linked with lymph node metastases, clinical staging and recurrence, and is regarded as an independent poor prognostic marker (71).

4. EMT signaling network regulated by DUB

EMT is an important biological mechanism whereby epithelial-derived tumor cells attain invasive and metastatic properties. In EC, DUBs provide a strict regulatory network by systematically adjusting the stability of EMT transcription factors and related effector molecules (Fig. 3).

Partial EMT and 'threshold control' by DUBs. Previous literature regards EMT as a binary process, in which cells shift from a completely epithelial state to a completely mesenchymal state. However, recent studies and single-cell sequencing data for ESCC have advanced the concept of 'partial EMT' (p-EMT) and 'hybrid EMT (72).

Tumor cells in the p-EMT state retain some epithelial characteristics, such as E-cadherin expression, while also developing specific mesenchymal qualities, including Vimentin and Snail expression. This hybrid condition confers cancer cells with significant adaptability, enabling them to sustain intercellular adhesion for collective migration, which is more effective for metastasis than solitary migration, while simultaneously resisting anoikis and chemotherapeutic agents.

DUBs may be crucial for maintaining the stability of this intermediate state. DUBs may stabilize cells in an aggressive, stem-like p-EMT state by regulating the protein levels of Snail or ZEB1 within a defined threshold, preventing their complete degradation (thus preserving mesenchymal characteristics), while also avoiding excessive accumulation (preventing total loss of epithelial adhesion) (73).

Regulation of major DUBs on the EMT signaling network. This section elucidates how principal DUBs facilitate the EMT process in ESCC by stabilizing essential substrates (Table II) (20,30,31,39,59,60,74-76). For example, USP26 stabilizes snail and represses transcription of the epithelial marker E-cadherin, initiating mesenchymal transition (74). OTUB1

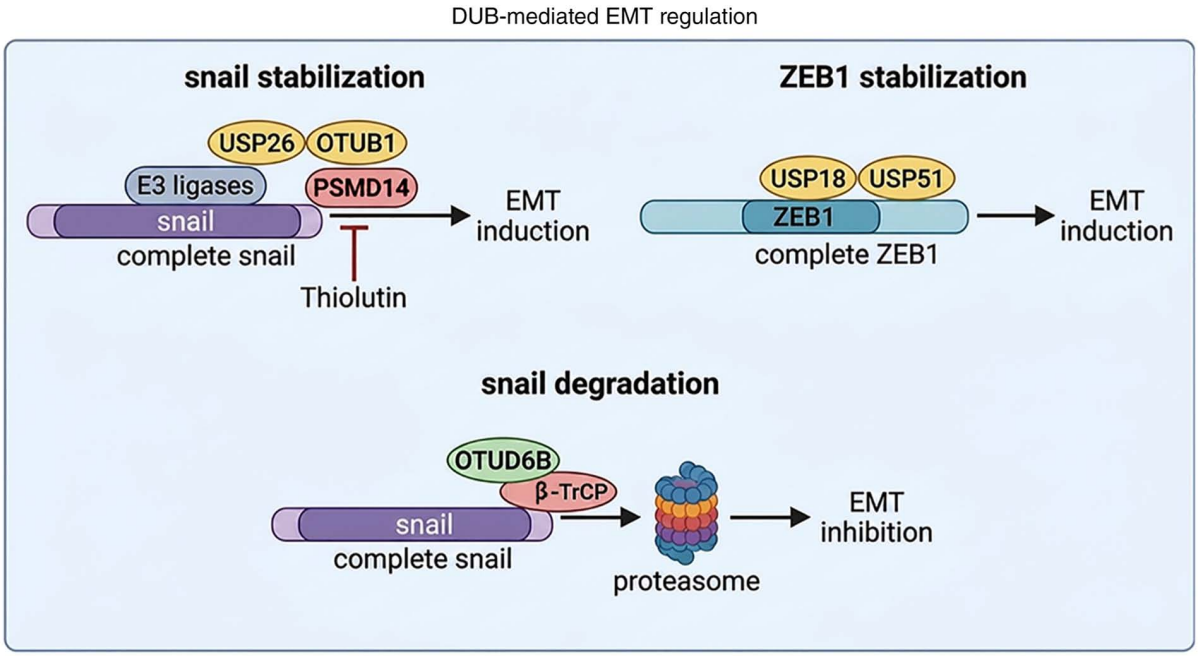

Figure 3. Mechanistic insights into DUB-regulated EMT. This figure illustrates the molecular mechanisms by which DUBs dictate cellular phenotypic plasticity through the post-translational regulation of EMT-inducing transcription factors. Stabilization of Snail and ZEB1: USP26, OTUB1 and PSMD14 cooperatively antagonize E3 ligase-mediated polyubiquitination to stabilize Snail. Similarly, USP18 and USP51 maintain ZEB1 protein levels, collectively triggering the induction of EMT. Proteasomal degradation of Snail: Conversely, OTUD6B recruits β-TrCP to facilitate the proteasomal degradation of Snail, thereby suppressing the EMT program and inhibiting tumor migration. Pharmacological intervention: Thiolutin exerts anti-metastatic potential by specifically inhibiting PSMD14-mediated Snail stabilization. EMT, epithelial-mesenchymal transition; DUB, deubiquitinating enzyme; USP, ubiquitin-specific protease; ZEB1, zinc finger E-box binding homeobox 1; OTUB1, ovarian tumour domain-containing Ub aldehydebinding protein 1; PSMD14, proteasome 26S subunit, non-ATPase 14; OTUD6B, ovarian tumor deubiquitinase 6B; β-TrCP, β-transducin repeats-containing proteins.

increases snail protein half-life, inducing the mesenchymal phenotype, and PSMD14 acts as a 19S proteasome subunit, 'rescuing' Snail before degradation to initiate EMT (59,60). Furthermore, USP18 induces EMT by accumulating ZEB1 (39), USP7 drives EMT in hypoxic microenvironments (20), OTUD6B stabilizes β-TrCP, leading to increased Snail degradation (75), USP10 indirectly activates EMT signaling via the MOF/ANXA2/Wnt pathway (30,31), USP51 drives EMT through ZEB1 and inhibits ferroptosis through GPX4 stabilization, promoting the survival of EMT cells (76).

5. The remodeling role of DUBs in the EC immune microenvironment

Immunosuppression in the tumor microenvironment (TME) is a primary cause of the limited effectiveness of immunotherapy for ESCC, such as anti-programmed cell death protein 1 (PD-1)/PD-L1 treatments. DUBs not only modulate tumor cell antigen presentation but also significantly influence the immune status of the TME by regulating the stability of immune checkpoint proteins.

Dynamic regulation of PD-L1 stability. The abundance of PD-L1 on tumor cell surfaces is a critical determinant of the effectiveness of anti-PD-1/PD-L1 treatments. DUBs directly determine the fate of PD-L1 via PTM.

USP7 and PD-L1. USP7 has been found to directly deubiquitinate PD-L1 in EC and other gastrointestinal neoplasms, thus inhibiting its breakdown via the proteasome pathway. Upregulated USP7 expression is positively associated with increased PD-L1 levels, leading to the inhibition of CD8+ T-cell cytotoxic function. USP7 inhibitors (e.g., P5091) can limit tumor cell proliferation and substantially decrease surface PD-L1 levels, thus restoring T-cell anti-tumor immune responses (77).

USP10 and long non-coding (lnc)RNA collaboration. The lncRNA forkhead box P4 antisense RNA 1 recruits USP10 to deubiquitinate and stabilize PD-L1 in EC, which directly leads to CD8+ T-cell exhaustion in the TME, promoting tumor immune evasion (32).

COP9 signalosome subunit 5 (CSN5; also known as COPS5) and inflammation-induced immunosuppression. CSN5 serves as an essential deubiquitinase for PD-L1. The TNF-α/NF-κB signaling pathway can enhance CSN5 expression, which subsequently maintains PD-L1 stability via deubiquitination, representing a crucial mechanism for inflammation-induced immunosuppression (77).

Regulation of cancer-associated fibroblasts (CAFs). DUBs not only directly act on immune checkpoints but also regulate stromal cells in the TME.

WISP1 and USP13. USP13 stabilizes WISP1, as previously stated. In ESCC, WISP1 is released by tumor cells and is also significantly expressed by CAFs. WISP1 remodels the extracellular matrix to facilitate collagen deposition, establishing physical barriers that inhibit T-cell infiltration while concurrently increasing tumor cell invasiveness (66).

Strategies for reshaping the immune microenvironment using the ubiquitination system. Based on the aforementioned

Table II. How major DUBs regulate the EMT signaling network in esophageal cancer.

DUB	Key target (substrate)	Regulatory mechanism	Specific impact on EMT network	Clinical/functional outcomes	(Refs.)
USP26	Snail (Snail1)	Removes Ub chains, preventing proteasomal degradation	Stabilizes Snail, represses transcription of the epithelial marker E-cadherin, initiating mesenchymal transition.	Promotes ESCC metastasis; negatively regulated by miR-203, forming the miR-203/USP26/Snail axis.	(74)
OTUB1	Snail	Directly binds and deubiquitinates	Increases Snail protein half-life, inducing the mesenchymal phenotype.	Predicts poor prognosis; the natural product Erianin can target and inhibit this axis.	(59,60)
PSMD14	Snail	Deubiquitinates Snail, enhancing its nuclear stability	Acts as a 19S proteasome subunit, 'rescuing' Snail before degradation to initiate EMT.	High expression correlates with short OS; the inhibitor Thiolutin can block this process.	(59,60)
USP18	ZEB1	Deubiquitinates and stabilizes ZEB1	ZEB1 accumulates, transcriptionally repressing E-cadherin, inducing EMT.	Promotes ESCC invasion and distant metastasis.	(39)
USP7	HIF-1α	Stabilizes HIF-1α	Drives EMT in hypoxic microenvironments; Pol ι can recruit USP7 to enhance this effect.	Promotes hypoxia-induced metastasis; acts synergistically with Pol ι.	(20)
OTUD6B	β-TrCP	Deubiquitinates the E3 ligase β-TrCP	Stabilizes β-TrCP (the E3 ligase for Snail), leading to increased Snail degradation.	Tumor suppressor; ATRA activates this axis to inhibit EMT.	(75)
USP10	ANLN, MOF	Stabilizes ANLN and MOF	Indirectly activates EMT signaling *via* the MOF/ANXA2/Wnt pathway.	Promotes cell division, proliferation, and metastasis.	(30,31)
USP51	ZEB1, GPX4	Stabilizes ZEB1; deubiquitinates GPX4	ZEB1 drives EMT; GPX4 stabilization inhibits ferroptosis, facilitating the survival of EMT cells.	Promotes growth and metastasis; inhibiting USP51 can induce ferroptosis.	(76)

DUB, deubiquitinating enzyme; EMT, epithelial-mesenchymal transition; Ub, ubiquitin; ESCC, esophageal squamous cell carcinoma; USPs, ubiquitin-specific proteases; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1; PSMD14, proteasome 26S subunit, non-ATPase 14; miR-203, microRNA-203; p53, tumor protein p53; HIF-1α, hypoxia-inducible factor 1α; OTUD6B, ovarian tumor deubiquitinase 6B; β-TrCP, β-transducin repeats-containing proteins; E3, ubiquitin ligase; Pol ι, DNA polymerase iota; MOF, males absent on the first; ANLN, anillin actin binding protein; ANXA2, annexin A2; OS, overall survival; Snail, Snail family transcriptional repressor 1; ZEB1, zinc finger E-box binding homeobox 1; GPX4, glutathione peroxidase 4.

mechanisms, strategies utilizing DUBs to regulate the immune system primarily include the following:

'Releasing the brake' strategy: Targeting PD-L1-associated DUBs. Specific inhibitors against USP7, USP10 or CSN5 can facilitate the Ub-mediated degradation of PD-L1. Despite activation by inflammatory factors such as IFN-γ, which typically increase PD-L1 transcription, these drugs operate at the protein level to significantly reduce PD-L1 levels on tumor cells, therefore sensitizing 'cold' tumors and improving the effectiveness of anti-PD-1/PD-L1 antibodies.

'Pro-polarization' strategy: Regulating macrophage phenotypes. DUBs also function within immune cells. For instance, USP7 inhibition can modulate the polarization state of tumor-associated macrophages, which stimulates their transition from the pro-tumorigenic M2 phenotype to the anti-tumorigenic M1 phenotype, thus improving the local immune microenvironment (78).

'Ignition' strategy: Inducing immunogenic cell death. Specific broad-spectrum DUB inhibitors, such as PR-619 and USP51 inhibitors, induce ER stress or ferroptosis, prompting tumor cells to release damage-associated molecular patterns, including ATP and HMGB1. These signals can recruit and stimulate dendritic cells, converting an environment with low immunogenicity into one with high immunogenicity, effectively changing 'cold' tumors into 'hot' tumors (60).

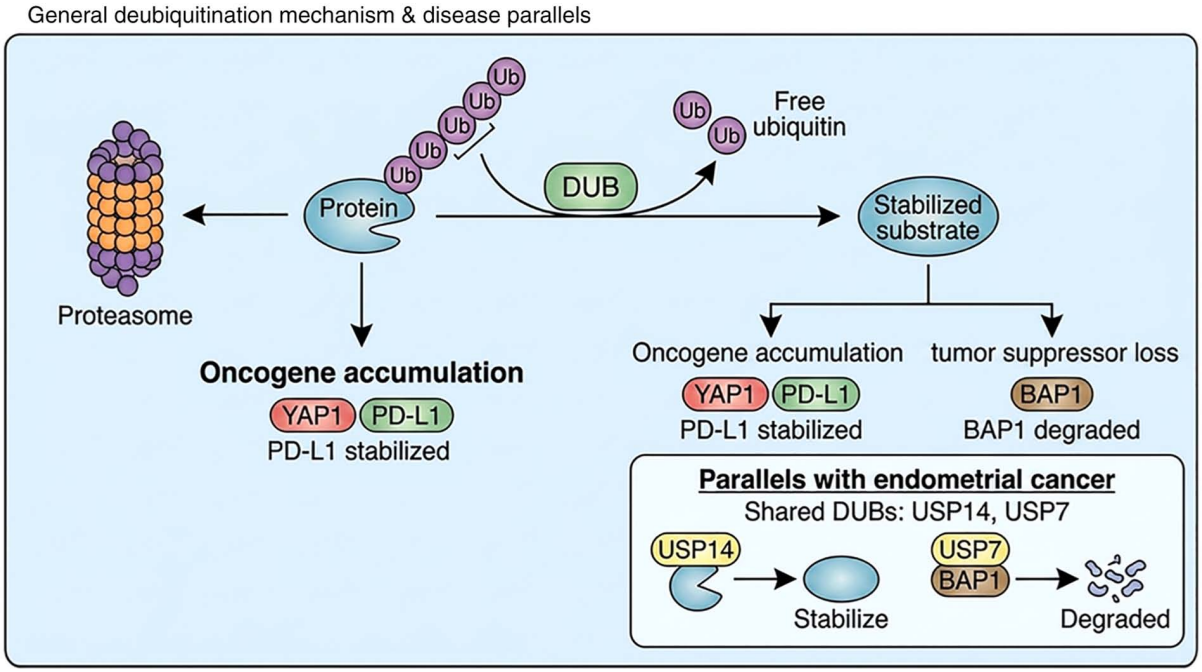

Figure 4. General deubiquitination mechanisms and pathological parallels in endometrial cancer. This summary diagram highlights the biochemical principles of deubiquitination and its clinical implications in malignancy, with a focus on endometrial cancer. Biochemical axis: DUBs cleave ubiquitin chains from target proteins, preventing their recognition and subsequent degradation by the 26S proteasome, thus ensuring substrate stability. Oncogenic imbalance: Dysregulated DUB activity leads to the pathological accumulation of oncogenes (e.g., YAP1 and PD-L1 stabilization via USP14) or the aberrant loss of tumor suppressors (e.g., USP7-mediated BAP1 degradation). Clinical relevance: In endometrial cancer, USP14 and USP7 are identified as pivotal regulatory hubs. They drive malignant transformation and immune evasion by maintaining the homeostasis of key pathological substrates, representing promising targets for precision oncology. DUB, deubiquitinating enzyme; USP, ubiquitin-specific protease; YAP1, Yes-associated protein 1; PD-L1, programmed death-ligand 1.

6. Another cancer mechanism comparison: Esophageal vs. endometrial cancer

Although esophageal and endometrial cancers differ vastly regarding anatomical site, tissue-embryological origin and core driving mechanisms (inflammation-driven vs. hormone-dependent), they display high consistency in their metabolic predispositions, such as obesity. This unique characteristic of being 'phenotypically distinct yet etiologically linked' provides an ideal model to explore the conservation and specificity of the deubiquitination regulatory network in tumor evolution. For a more comprehensive understanding of DUBs' functional conservation and specificity, DUBs' regulatory mechanisms in EC and uterine corpus endometrial carcinoma were detailed and compared (Fig. 4).

Identified DUBs and their mechanisms in endometrial cancer. Endometrial cancer is a prevalent gynecological malignancy, exhibiting both similarities and marked differences in its molecular features compared to EC.

USP14. In endometrial cancer, USP14 is a high-risk predictor of recurrence. It has been found to promote cell proliferation by stabilizing IκB-α's upstream kinases or acting directly on NF-κB pathway components. Furthermore, high USP14 levels are substantially linked with increased Ki67 index (a proliferation marker) (68).

USP7. In endometriosis and malignant transformation, USP7 preserves the methylated silenced state of tumor suppressor genes by maintaining DNA methyltransferase 1 (DNMT1) and EZH2 via deubiquitination, facilitating aberrant cellular proliferation (79).

BAP1. The absence of BAP1 is a characteristic feature of high-grade endometrial cancer and uterine carcinosarcoma, frequently signifying early recurrence and unfavorable prognosis. The loss of BAP1, functioning as a tumor suppressor, results in impaired DNA damage repair mechanisms and aberrant cell differentiation (80).

Comparative analysis: Commonalities and differences

The core oncogenic status of USP14 (commonality). In both esophageal and endometrial cancer, USP14 acts as a significant oncogene and an indicator of poor prognosis. In endometrial cancer, it is primarily linked to radiation resistance (via YAP1) and EMT; it is predominantly correlated with recurrence and proliferation (through NF-κB). This suggests that USP14 is a therapeutic target with broad applicability, and its inhibitors (such as VLX1570 and Degrasyn) may be beneficial for both malignancies.

Epigenetic regulation by USP7 (commonality). USP7 functions by stabilizing epigenetic modifying enzymes (EZH2, DNMT1) across various cancers, suggesting that targeting USP7 to suppress tumors by remodeling the epigenetic landscape is a conserved cross-cancer mechanism.

Functional differences and complexity of BAP1. In endometrial cancer, BAP1 predominantly demonstrates typical tumor suppressor gene loss. However, in EC, although BAP1 mutation rates are higher and can enhance proliferation in certain cell lines, certain studies suggest that particular

Table III. Preclinical research data of small molecule inhibitors targeting DUBs in esophageal cancer.

Inhibitor	Target DUB	Experimental system (model)	Key quantitative metric (IC_{50}/inhibition rate/P-value)	Functional outcome	(Refs.)
P5091	USP7	*In vitro* (ESCC cell lines: KYSE30, 450)	EC_{50} ≈4.2 μM (enzyme activity); significant cell proliferation inhibition (P<0.01)	Induces NOXA-mediated apoptosis; arrests cell cycle at G2/M phase	(22)
P5091	USP7	*In vivo* (CT26/ESCC xenograft)	Tumor volume significantly reduced (vs. the control group, P<0.05); PD-L1 was downregulated	Inhibits tumor growth, enhances T-cell infiltration and synergizes with anti-PD-1	(78)
Thiolutin (THL)	PSMD14	*In vitro* (ESCC cells: KYSE30, 150)	IC_{50}: 0.60 μM (KYSE30), 1.12 μM (KYSE150)	Inhibits Snail deubiquitination, reverses EMT and downregulates N-cadherin	(60)
Thiolutin (THL)	PSMD14	*In vivo* (nude mouse subcutaneous tumorigenesis)	Tumor volume inhibition rate >50% (P<0.05); Snail protein levels decrease	Inhibits tumor growth and metastasis, significantly sensitizes cisplatin treatment	(60)
Degrasyn (WP1130)	USP14, USP9X, USP5	*In vitro* (EC109, KYSE510)	IC_{50}: ~0.3-2.5 μM (cell line dependent)	Downregulates YAP1, induces DNA damage, enhances radiotherapy sensitivity	(83)
Degrasyn (WP1130)	USP14	*In vivo* (xenograft model)	Tumor volume in the combined radiotherapy group was significantly smaller than that in the monotherapy group (P<0.01)	Reverses *in vivo* radiation resistance without obvious systemic toxicity	(17)
PR-619	Pan-DUB	*In vitro* (KYSE 30, 450)	IC_{50}: 5-20 μM (48 h treatment)	Induces G2/M arrest, triggers ER stress-mediated apoptosis	(81)
ML323	USP1	*In vitro* (ESCC cells)	IC_{50}: 0.076 μM (highly effective against USP1)	Inhibits cell proliferation, induces genomic instability	(82)

DUB, deubiquitinating enzyme; EMT, epithelial-mesenchymal transition; THL, thiolutin; IC50, half maximal inhibitory concentration; EC50, half maximal effective concentration; P (P-value), probability value; G2/M phase, growth 2/mitosis phase; NOXA, PMAIP1 (phorbol-12-myristate-13-acetate-induced protein 1)/NOXA; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PSMD14, proteasome 26S subunit, non-ATPase 14; USP, ubiquitin-specific protease; Snail, Snail family transcriptional repressor 1; YAP1, Yes-associated protein 1.

mutations (such as F170I) may confer oncogenic characteristics or cause the loss of tumor suppressive capabilities (53-56). This suggests that BAP1's function in EC may be contingent upon context or specific mutations, rendering it more intricate than in endometrial cancer.

Hormonal regulation specificity. Research on endometrial cancer highlights the significance of deubiquitinating enzymes in hormone receptors and associated pathways, while EC studies concentrate more on environmental stressors, such as hypoxia and radiation, as well as EMT.

7. Prospects of therapeutic targets, inhibitors and preclinical data

Most promising DUB therapeutic targets. Based on comprehensive mechanistic research, the degree of correlation with key oncogenic pathways and the availability of inhibitors, the following DUBs were identified as the most promising targets in EC treatment (Table III).

USP7. USP7 is located at the crossroads of P53-MDM2, epigenetic (EZH2/DNMT1), and immune (PD-L1) regulation.

Its inhibition can simultaneously achieve a 'kill three birds with one stone' effect by stimulating P53-dependent apoptosis, inhibiting epigenetic drivers and promoting anti-tumor immunity (21,77,79).

USP14. Because of its close association with proteasome processes and its dual modulation of YAP1 and NF-κB, USP14 demonstrates significant potential, particularly in reversing radiation resistance in EC (17,68).

PSMD14. PSMD14's specific modulation of Snail within the 19S proteasome renders it a crucial target for inhibiting metastasis in EC (59,60).

Preclinical quantitative data of DUB inhibitors. This section delineates the principal quantitative measurements of significant DUB inhibitors in experimental systems for EC to illustrate their efficacy levels (Table III). For example, Thiolutin inhibits tumor growth and metastasis, significantly enhancing cisplatin treatment sensitivity (60). P5091 can regulate the cell growth cycle and act synergistically with anti-PD-1 (22,78). There are also various other inhibitors that can exert their effects by inhibiting cell growth or increasing sensitivity to radiotherapy (17,81-83). For example, as a USP14 inhibitor, Degrasyn can work by enhancing radiosensitivity and reversing radiation resistance in the body (17,83). The inhibitors PR-619 and ML323 work by messing with the cell growth cycle (81,82).

Development challenges

Selectivity and off-target effects. Most DUBs share a highly conserved cysteine protease catalytic domain, resulting in early inhibitors (such as PR-619 and WP1130) frequently indicating broad-spectrum activity and insufficient subtype specificity. This complicates the identification of specific drug mechanisms that inhibit a single DUB and increase the risk of off-target damage (14).

Toxicity and safety. The ubiquitination system is responsible for maintaining fundamental protein homeostasis in normal cells. Systemically inhibiting DUBs (especially DUBs intimately linked with proteasome function, like USP14) may trigger side effects similar to proteasome inhibitors (like bortezomib), including neurotoxicity and cytotoxicity.

Pharmacokinetic properties. Multiple current DUB inhibitors have poor water solubility and low bioavailability, which limits their clinical administration methods and efficacy (84).

Lack of clinical biomarkers. Despite the identification of various highly expressed DUBs in EC, there is currently a lack of standardized clinical testing methods, such as Companion Diagnostics immunohistochemical (IHC) scoring criteria (85), to effectively identify patient populations that would benefit from DUB inhibitors.

8. Key knowledge gaps and questions

Despite considerable advancements in the study of DUBs in EC, bridging a gap from laboratory findings to clinical application necessitates addressing the following critical limitations:

Scarcity of patient-derived model validation. The major portion of existing data is based on immortalized EC cell lines, such as the KYSE series (86). There is insufficient validation of DUB inhibitors in patient-derived xenograft (PDX) models or patient-derived organoids. Since these models effectively maintain the heterogeneity and microenvironmental traits of the underlying tumor, the insufficient data on these models limit the predictive accuracy of the clinical efficacy of medicines (87).

Missing PTM regulatory maps for DUBs. The data on how DUBs modulate their substrates are insufficient, and even less on how DUBs themselves are regulated by PTM (such as phosphorylation, acetylation, oxidation, ubiquitination) (18,88,89). For example, EC cells are often under oxidative stress; however, the effects of reactive oxygen species on active cysteine residues, thus altering DUBs activity, have not been comprehensively investigated (90,91).

Neglect of non-catalytic functions. Certain DUBs may exhibit non-catalytic roles, such as serving as scaffold proteins in complex assembly (18,92). Current inhibitors predominantly focus on the catalytic active site and may fail to inhibit non-enzymatic processes, leading to ineffective therapy (93).

Limited translational research on clinical biomarkers. In addition to fundamental expression level correlation analyses, prospective research on DUB mutations, splice variants or certain PTM states as predictive indicators of treatment efficacy is also limited (94-98).

9. Conclusion

In summary, DUBs are the key regulators of the onset, malignant progression, treatment resistance and immune evasion of EC. DUBs intricately regulate signaling pathways such as TGF-β, Wnt and NF-κB, as well as the stability of crucial oncoproteins including Snail, YAP1 and PD-L1, forming a complex oncogenic network. USP7, USP14 and PSMD14 demonstrate significant potential as therapeutic targets due to their critical roles in numerous carcinogenic pathways and the availability of previous inhibitor data.

Comparative analyses with endometrial cancer further validated the role of certain DUBs (such as USP14) as general prognostic markers for poorer prognosis, while also highlighting their functional specificity in distinct tissue environments. Current DUB inhibitors (e.g., P5091, Thiolutin and Degrasyn) have promising anti-tumor efficacy and sensitizing effects to chemotherapy and irradiation in preclinical models, specifically Thiolutin, which achieved an *in vivo* tumor inhibition rate exceeding 50%, and Degrasyn's ability to reverse radiation resistance (17,22,60,78,83).

However, translating these insights into clinical advantages requires addressing the selectivity challenges of inhibitors and performing thorough validation in PDX or organoid models that more accurately replicate clinical conditions (94). Future research must concentrate on developing highly selective allosteric inhibitors, utilizing innovative technologies such as proteolysis targeting chimera/deubiquitinase-targeting chimera to degrade or target DUBs (99,100), and investigating targeted immune combination therapy strategies informed by

DUB expression profiles, to overcome the persistent challenge posed by EC (19).

Although organoids offer benefits in primary *in vitro* efficacy assessment, PDX models are essential for investigating the effects of DUBs on tumor angiogenesis, distant metastasis and systemic pharmacokinetics (101). By directly implanting patients' tumor tissue into immunodeficient mice (such as NOD-Prkdcem26Il2rgem26/Gpt or NOD scid gamma), PDX provides the same stromal architecture and intercellular connections (102).

The oncogenic roles of Josephin domain containing 2 (JOSD)2 and PSMD14 have been thoroughly confirmed in PDX models within ESCC research. For instance, JOSD2 knockdown can significantly limit volumetric expansion in PDX tumors and enhance tumor susceptibility to chemotherapeutic agents (61). Furthermore, PDX models serve as the gold standard for evaluating *in vivo* target engagement of allosteric inhibitors that target the non-catalytic functions of DUBs. Utilizing activity-based protein profiling in conjunction with mass spectrometry, researchers can quantitatively assess the extent to which an inhibitor restricts the specific *in vivo* activity of a DUB (103).

The development of humanized PDX models has emerged as a leading approach to more accurately replicate the immune microenvironment. Researchers can ascertain whether DUB inhibitors, such as USP14 inhibitors, alter tumor development dynamics by altering CAFs or influencing macrophage polarization by transplanting human hematopoietic stem cells or peripheral blood mononuclear cells to reconstruct the murine immune system (95,98). Furthermore, to ensure accurate clinical use of DUB inhibitors, it is essential to develop a standardized protocol comprising antibody validation, scoring systems, clinical threshold determination and multi-indicator joint detection (104).

Companion diagnostics can identify the patient populations most likely to benefit from specific DUB inhibitors. For instance, the Food and Drug Administration's Combined Positive Score standard for PD-L1 expression has become the criterion for the administration of pembrolizumab in ESCC (105,106). Future research for developing DUB inhibitors should establish a 'DUBome panel' that comprehensively categorizes patients by including the mRNA or protein expression profiles of 10-20 essential DUBs (107,108).

Accurate prognostic prediction models can be developed by integrating IHC data with gene microarray or next-generation sequencing results, and employing Artificial Intelligence methods for dimensionality reduction (109-111). This multimodal integrated analysis can reveal patients with moderate single-target expression but significantly elevated pathway activity, thus broadening the pool that may benefit (112-114).

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Authors' contributions

YZ and CH provided the theoretical basis and wrote the manuscript. KC conducted a literature search. NS and RH classified and organized the literature. GL reviewed the manuscript. All authors read and approved the final version of the manuscript. Data authentication does not apply.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

Artificial intelligence tools (Google Gemini; Gemini 3.0 pro; https://gemini.google.com) were used to assist in figure legend drawing.

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