USP10 deubiquitinase: Physiological function, diseases and therapeutic target (Review)

LINLIN ZHANG[1], HUAJING SUN[2], ZIFAN WANG[1], ZHIMEI WANG[3], QIANG MU[2] and YUKUN LIU[2]

[1]Department of Oncology and Radiotherapy, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong 266000, P.R. China; [2]Department of Breast Surgery, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong 266000, P.R. China; [3]Department of Gynecological Oncology, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong 266000, P.R. China

Received October 31, 2025; Accepted January 27, 2026

DOI: 10.3892/ijmm.2026.5807

Abstract. Ubiquitination is crucial for regulating diverse cellular functions, including protein degradation, cell cycle progression, signal transduction and gene expression. This intricate process is mediated by the ubiquitin proteasome system. Within this system, ubiquitin-specific protease 10 (USP10) is a key member that, through its deubiquitinase activity, orchestrates multiple cellular processes, such as DNA damage repair, immune and inflammatory responses, environmental adaptation and autophagy. The biological activity and protein stability of USP10 are extensively regulated by post-translational modifications, including PARylation, histone methylation and ubiquitination. Functionally, USP10 has a dual role in tumorigenesis: It can either promote or suppress cancer progression and metastasis by influencing oncogenic signaling pathways. Beyond cancer, USP10 has been implicated in the pathogenesis of cardiovascular and neurodegenerative diseases, as well as organ fibrosis, underscoring its broad physiological relevance. Decades of research have spurred the development of a range of USP10 inhibitors, such as Spautin-1, P22077, HBX19818, Wu-5 and D1. The present review provides a comprehensive overview of recent advances in understanding the role of USP10 in maintaining homeostasis and dissects the pathological mechanisms in human diseases. The review further highlights the potential of precise USP10-targeted interventions as promising therapeutic strategies for disease prevention and treatment.

Correspondence to: Professor Qiang Mu or Professor Yukun Liu, Department of Breast Surgery, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, 127 Siliu South Road, District of Shibei, Qingdao, Shandong 266000, P.R. China
E-mail: mudoctor@163.com
E-mail: liuyukun19900813@126.com

Key words: deubiquitinase, USP10, physiological function, therapeutic target

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1. Introduction

The expression and activity of protein are tightly controlled by epigenetic processes, particularly post-translational modifications. Among these, ubiquitination is a highly conserved and reversible modification that covalently attaches ubiquitin molecules to target proteins, thereby modulating their stability, activity, localization and interactions (1). Ubiquitination is essential in diverse physiological and pathological processes, including protein degradation, cell cycle regulation, signal transduction, gene expression and autophagy (2,3). The ubiquitin-proteasome system (UPS) is the principal pathway for intracellular protein degradation and regulation. It consists of ubiquitin, ubiquitin-activating enzymes (E1), conjugating enzymes (E2), ligases (E3), deubiquitinating enzymes (DUBs) and the 26S proteasome. In eukaryotes, 80-90% of protein degradation depends on the UPS, which is mediated through a sequential enzymatic cascade (4). Ubiquitin contains seven lysine residues (K6, K11, K27, K29, K33, K48 and K63) and one N-terminal methionine residue (Met1), which can be used to form ubiquitin chains. Notably, ubiquitin can form monomer ubiquitin chains or polyubiquitin chains (such as K48 and K63). Different types of ubiquitin chains can regulate different cellular processes (5). For instance, the K48 chain is usually labeled with protein for degradation (6), while the K63 chain is involved in signal transduction (7). K6 chain are associated with autophagy and DNA damage response. K11 chain participates in cell-cycle regulation and proteasomal degradation. K27 chain is implicated in protein secretion and innate immunity. K29 chain has a role in neurodegenerative disorders. K33 chain can influence protein trafficking (8,9). Notably, in contrast to the well-characterized K48 and K63-linked

chains, these atypical ubiquitin linkages remain comparatively understudied. Initially, ubiquitin is activated by E1 in an ATP-dependent manner, transferred to the cysteine residue of E2, and subsequently conjugated to substrate proteins via E3 ligases, resulting in substrate ubiquitination (10).

DUBs represent a major branch of the ubiquitin system. They contain ubiquitin-binding motifs that facilitate the recognition and recruitment of ubiquitinated proteins, thereby ensuring specificity and precise regulation (11). While ubiquitin attachment is mediated by the E1/E2/E3 enzymatic cascade, DUBs reverse this process by cleaving peptide or isopeptide bonds between ubiquitin and its substrates. This deubiquitination not only stabilizes proteins but also fine-tunes signaling cascades, preventing excessive activation and maintaining ubiquitin system homeostasis (12,13). There are ~100 DUBs known in humans and they are categorized into seven families: Ubiquitin-specific proteases (USPs), ovarian tumor proteases, Josephins and JAB1/MPN/Mov34 metalloenzymes, Machado-Joseph disease protein domain proteases, ubiquitin carboxy-terminal hydrolases (UCHs), motif-interacting with ubiquitin-containing novel DUB family and the zinc finger-containing ubiquitin peptidase 1 (14). USPs are indispensable for regulating critical biological functions such as DNA damage and repair, metabolism, cellular differentiation, epigenetic modulation and protein stability (15-18). USP10 dysregulation has been associated with multiple human diseases, including inflammatory disorders and infections (19-21), cardiovascular disease (22-24) and neurodegeneration (25-27). Alterations in the expressions of USPs have also been observed in cancers, which suggests that these proteins are involved in tumorigenic mechanisms (28-31).

USP10, a deubiquitinase that interacts with Ras-GAP SH3-domain-binding proteins, was first described by Soncini *et al* (32) in 2001, and subsequent research has progressively revealed its diverse biological functions (Fig. 1). There have been reports that USP10 modulates p53 stability (33,34), autophagy (35,36), DNA damage response (DDR) (37-39) and cellular energy metabolism (40,41). While early studies primarily focused on its oncogenic roles in specific cancers, more recent findings highlight its broader biological functions, regulatory mechanisms and pathological relevance across multiple diseases. The present review offers a comprehensive overview of USP10 biology, with particular emphasis on its mechanistic links to human diseases and its potential as a therapeutic target, offering new perspectives for cancer and beyond.

2. Characteristics of USP10

Structure and cellular localization. USP10, also known as UBPO, is located on human chromosome 16q24.1 (42) and consists of 18 exons. The human USP10 protein is comprised of 798 amino acids (AAs), with a molecular weight of ~93 kDa (32). Its molecular structure (Fig. 2A) is composed of three domains: A RasGAP SH3 domain binding protein stress granule assembly factor 1 (G3BP1)-interacting motif, an N-terminal domain and a USP catalytic domain. The full-length model of USP10, predicted by AlphaFold (43,44), is shown in Fig. 2B. The USP domain can be divided into three subdomains: Finger, thumb and palm (45). The finger subdomain mediates engagement of the distal ubiquitin moiety within polyubiquitin chains, whereas the active site is formed at the thumb-palm interface and comprises a conserved catalytic triad of Cys, His and Asp/Asn residues (45). The catalytic core contains six conserved boxes found across nearly all USP family members (Fig. 2C). Boxes 1, 5 and 6 harbor the catalytic cysteine, histidine and aspartate/asparagine residues, respectively. Boxes 3 and 4 contain a Cys-X-X-Cys zinc-binding motif, which promotes proper USP core folding and facilitates interactions among motifs separated by hundreds of residues. The results of multiple sequence alignment show that the catalytic triad of USP10 may consist of Cys424, His749 and Asp766 (46).

USP10 is evolutionarily conserved, sharing ~99% AA sequence homology with its mouse counterparts, and is broadly expressed in both the nucleus and cytoplasm of most cell types. Expression of USP10 has been detected in multiple human tissues, such as brain, kidney, adrenal gland, breast and stomach (47). The highest RNA expression of USP10 is observed in skeletal muscle (Fig. 3) according to the Human Protein Atlas (https://www.proteinatlas.org). Abnormal upregulation of USP10 has been reported in several cancer types, including osteosarcoma (36), breast cancer (48), pancreatic ductal adenocarcinoma (PDAC) (49), colorectal cancer (CRC) (50), prostate cancer (51), non-small cell lung cancer (NSCLC) (52), ovarian cancer (52), glioblastoma (GBM) (53), esophageal squamous cell carcinoma (ESCC) (54) and head and neck squamous cell carcinoma (55). Notably, USP10 expression is also found in lower eukaryotes such as yeast (56), where its homolog, UBP3, is essential for DNA repair (57).

The subcellular localization of USP10 is highly dynamic and context-dependent. Under non-stressed conditions, USP10 is predominantly cytoplasmic, where it functions as a deubiquitinase to stabilize and enhance p53 activity. Following DNA damage and ATM serine/threonine kinase (ATM) activation, USP10 becomes phosphorylated and translocates to the nucleus, where it cooperates with USP7 to deubiquitinate and stabilize p53 (34). This nucleo-cytoplasmic shuttling is essential for USP10 to access and regulate compartment-specific substrates such as nuclear p53. Additional research has demonstrated that AKT-mediated phosphorylation of USP10 at Thr764 within its nuclear localization signal promotes nuclear translocation (58). More recently, Liu *et al* (38) demonstrated that oxaliplatin treatment markedly increases the nuclear expression of USP10 in CRC cells. Nuclear USP10 enhances CRC proliferation, oxaliplatin resistance and DNA repair by stabilizing XPA binding protein 2 (XAB2). Notably, although USP10 nuclear translocation can be induced by ATM-mediated phosphorylation (Thr42/Ser337) following stress and by AKT-mediated phosphorylation (Thr764) under chemotherapeutic exposure, current evidence does not support a sequential or hierarchical relationship between these pathways. Instead, ATM and AKT appear to regulate USP10 localization through distinct, context-dependent mechanisms, and it remains unclear whether they interact or compensate for each other in specific disease settings such as oxaliplatin-treated CRC. In summary, these findings indicate that USP10 localization is highly plastic and sensitive to external stimuli, including DNA damage and chemotherapeutic stress.

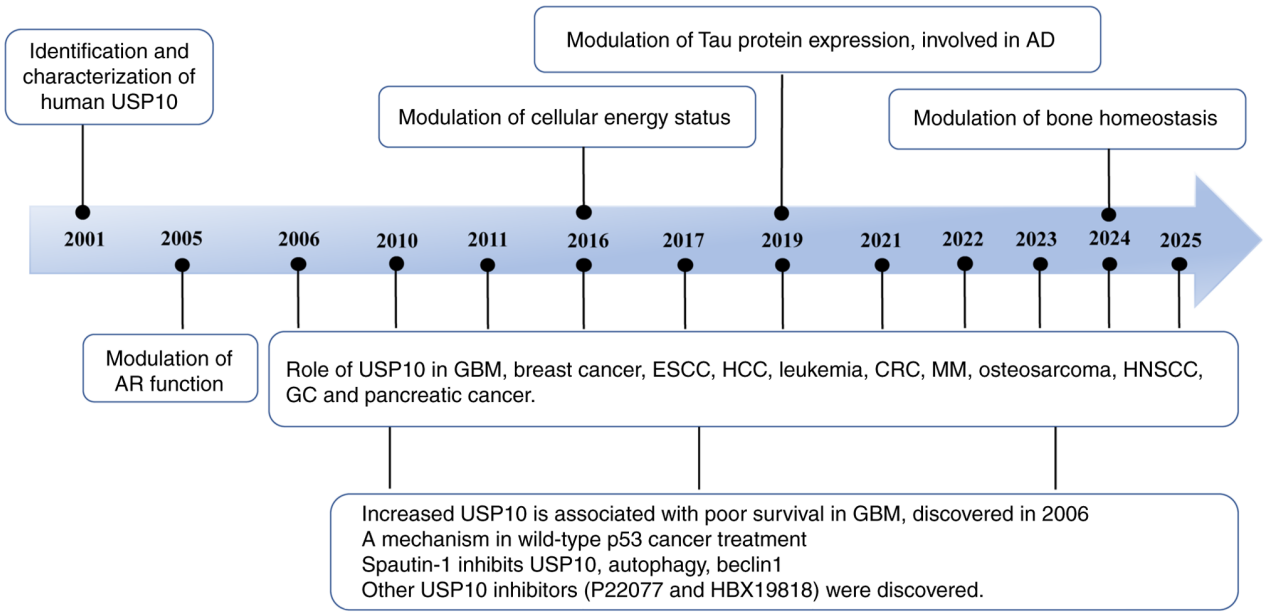

Figure 1. Timeline of USP10 research. A large number of related studies on diseases and treatments are listed to show the importance of USP10 research. AD, Alzheimer's disease; AR, androgen receptor; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MM, multiple myeloma; GBM, glioblastoma; HNSCC, head and neck squamous cell carcinoma; USP, ubiquitin-specific protease.

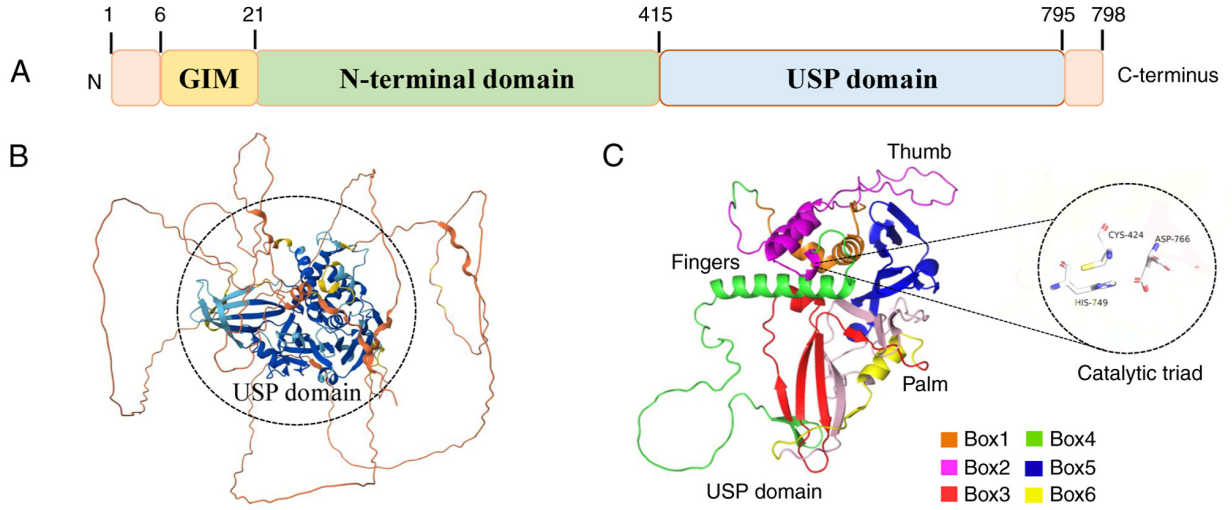

Figure 2. USP10 structural schematic diagram. (A) USP10 structural schematic diagram; USP10 contains a short N-terminal GIM (residues 6-21), N-terminal (residues 21-415) and a well-folded C-terminal USP catalytic domain (residues 415-795). (B) USP10 full-length model. The model is color-coded by pLDDT confidence scores according to the AlphaFold standard. Dark blue (pLDDT >90): Very high confidence, indicating well-modeled, rigid regions; light blue/cyan (pLDDT 70-90): Confident, indicating generally reliable backbone prediction; yellow (pLDDT 50-70): Low confidence, suggesting flexible or partially disordered regions; orange (pLDDT <50): Very low confidence, typically corresponding to intrinsically disordered regions. (C) The six conserved boxes and catalytic triad of USP10. Six colors represent six conserved boxes. Available online: https://alphafold.ebi.ac.uk/entry/Q14694. GIM, G3BP1-interacting motif; USP, ubiquitin-specific protease.

Physiological function of USP10

DNA damage and repair. DDR is a sophisticated protein network that coordinates DNA repair with cell-cycle checkpoints to protect cells from genomic insults (59). Increasing evidence indicates that USPs are key regulators of DDR, acting through deubiquitination of critical mediators such as p53, checkpoint kinase 2 (CHK2) and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5 (60-64). For example, Zhu *et al* (65) reported that USP33 stabilizes p53 via deubiquitination, thereby modulating the DDR. Similarly, USP39 enhances DNA damage repair and radioresistance by stabilizing CHK2 (66).

MutS homolog 2 (MSH2), a central DNA mismatch repair protein, is essential for genomic stability. A previous study showed that USP10 deubiquitinates and stabilizes MSH2, thereby influencing cellular sensitivity to DNA damage (37). Recent findings revealed that USP10 binds to XAB2 and removes ubiquitin at Lys593, preventing proteasome-mediated degradation and stabilizing the protein. Stabilized XAB2 upregulates annexin A2 (ANXA2) transcription by binding to

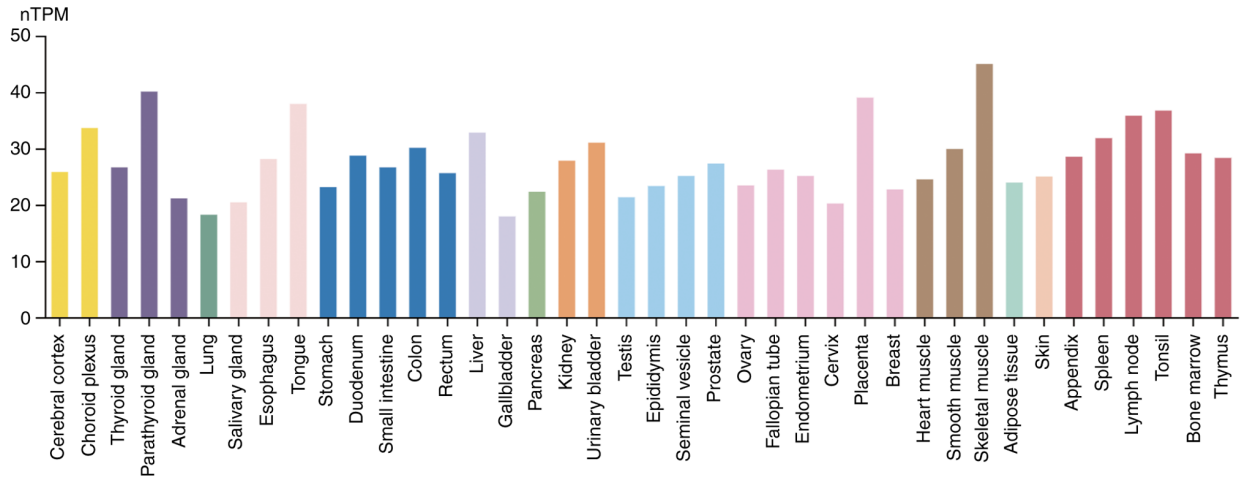

Figure 3. RNA expression levels of ubiquitin-specific protease 10 in various tissues of human body. Different bar colors represent distinct organ systems. Available online: https://www.proteinatlas.org/ENSG00000103194-USP10/tissue.

its promoter, thereby facilitating CRC cell growth, DDR activation, oxaliplatin-induced DNA repair and chemoresistance (38). Additional evidence further links USP10 to therapeutic resistance. Zhao *et al* (67) showed that astrocyte elevated gene-1 (AEG-1) mitigates radiation-induced DNA damage and enhances radioresistance in ESCC. Mechanistically, AEG-1 recruits USP10 by removing K48-linked polyubiquitin chains from poly(ADP-ribose) polymerase 1 (PARP1) at Lys425 to prevent its proteasomal degradation. This stabilization facilitates homologous recombination-mediated repair of DNA double-strand breaks, ultimately reducing DNA damage and conferring resistance to irradiation (67).

Autophagy and stress granule (SG) formation. Autophagy is an essential mechanism for preserving cellular homeostasis, contributing to environmental adaptation, pathogen clearance, aging delay and energy stress responses. USP10 participates in autophagy activation by modulating the activity of autophagy-related molecules such as microtubule-associated protein 1 light chain 3b (LC3B) and Beclin1. Under starvation stress in neonatal mice, USP10 promotes survival by removing ubiquitin modifications from murine double minute 2, thereby enhancing its E3 ligase activity toward p53 and inducing autophagy (33). USP10 also deubiquitinates LC3B, resulting in increased LC3B levels and enhanced autophagy (35). Furthermore, Liu *et al* (68) demonstrated that USP10 stabilizes Beclin1 by preventing its ubiquitin-mediated degradation, thereby facilitating autophagy.

SGs are cytoplasmic condensates in eukaryotic cells, with G3BP1/2 identified as critical regulators of their assembly. USP10 is essential to SG dynamics by interacting with G3BPs, thus regulating their formation and disassembly (69). Recently, Tahmasebinia *et al* (70) showed that the USP10-G3BP1 complex functions as a central hub interfacing with pathways such as energy metabolism, enabling fine-tuning of mitochondrial homeostasis and rapid adaptation to environmental stimuli.

Male function. A previous study identified USP10 as a transcriptional coactivator of androgen receptor (AR)-regulated genes, where it binds AR and enhances androgen-responsive promoter activity (71). Recent findings revealed that USP10 and sirtuin 6 (SIRT6) work together to preserve spermatogonial proliferation and DNA repair capacity, thereby providing critical protection against spermatogenic defects induced by microcystin-LR (72). USP10 also regulates the stability of G3BP1, a core component of SGs, thereby influencing their assembly and disassembly. This mechanism helps maintain SG homeostasis in supporting cells and ensures normal spermatogenesis. Furthermore, USP10 modulates SG dynamics in the presence of pathological protein variants, such as fused in sarcoma^{R521C}, linking USP10 to male fertility and the pathogenesis of related reproductive disorders (73).

Inflammation and immune response. There is evidence that USP10 serves a notable role in regulating immune and inflammatory responses (74,75). In a mouse model of cerebral ischemia-reperfusion (I/R) injury, USP10 was shown to promote neuroinflammation through activation of the NF-κB signaling pathway (74). Conversely, USP10 binds the nuclear T-box transcription factor T-bet, stabilizing it through deubiquitination and thereby alleviating type 2 T-helper cell-dominant inflammation in asthma (76). Retinoic acid inducible gene-I (RIG-I) recognizes viral RNA and triggers robust antiviral responses by inducing type I interferon production. To transmit RIG-I-mediated signaling, the mitochondrial adaptor mitochondrial antiviral signaling protein (MAVS) assembles into prion-like aggregates that activate downstream kinases and transcription factors (77). Liu *et al* (78) demonstrated that USP10 removes unanchored K63-linked polyubiquitin chains from MAVS, thereby suppressing RIG-I-mediated MAVS aggregation. Consistently, USP10-deficient mice displayed increased resistance to RNA virus infection. Previously, USP10 has been shown to regulate humoral immunity. By deubiquitinating activation-induced cytidine deaminase (AID), USP10 modulates neutralizing antibody production following nanoparticle vaccination against severe acute respiratory syndrome coronavirus 2 and human immunodeficiency virus type 1 (58).

Bone homeostasis and hematopoiesis. Zhou *et al* (79) have shown that USP10 regulates bone homeostasis by deubiquitinating nuclear receptor subfamily 3 group C member 1 (NR3C1), thereby controlling cystatin-3 expression. Silencing USP10 suppresses osteoclast differentiation in RAW264.7 cells and bone marrow-derived macrophages, while simultaneously

promoting osteogenic differentiation in MC3T3-E1 cells. S-phase kinase associated protein 2 (SKP2) was found to be a negative regulator of osteogenesis in earlier research (80). Notably, USP10 enhances SKP2 stability and promotes its expression, suggesting a context-dependent role in bone remodeling (81). In addition, USP10 expression is upregulated by bone morphogenetic protein 9 (BMP9), a potent osteogenic factor. USP10 subsequently removes K48-linked ubiquitin chains from forkhead box (FOX)O1, preventing its excessive cytoplasmic ubiquitination. Stabilized FOXO1 accumulates in the cytoplasm and eventually translocates back to the nucleus, where it contributes to the pathogenesis of osteoporosis (82). Beyond skeletal regulation, USP10 is also essential for hematopoiesis. It protects hematopoietic stem and progenitor cells, including long-term hematopoietic stem cells, from apoptosis, underscoring its role in maintaining hematopoietic integrity (83).

Signal transduction regulation. Cell signaling is the process by which chemical or physical cues are transmitted through a cascade of molecular events, ultimately contributing to the expression of specific genes and consequent biological responses such as proliferation and apoptosis (84). Numerous signaling pathways have been identified to be regulated by USP10, including Notch (85), TGF-β (86), NF-κB (87,88), Wnt (89), Hippo (90,91) and PI3K/AKT (92). Specifically, USP10 removes ubiquitin chains from αv-integrin, resulting in its accumulation on the cell surface, subsequent activation of TGFβ1 signaling and pathological differentiation of myofibroblasts (93). The role of USP10 in modulating these signaling pathways has been comprehensively reviewed by Chen *et al* (94). Taken together, USP10 exerts critical regulatory functions across diverse cellular processes, including DNA damage repair, autophagy, immune responses and signal transduction.

3. Regulation of USP10 expression

Such as most deubiquitinases, USP activity may be modulated through numerous mechanisms at both transcriptional and post-translational levels. Similarly, USP10 expression is tightly controlled by phosphorylation, histone methylation, ubiquitination, PARylation and transcriptional regulation (Fig. 4). Elucidating these regulatory mechanisms may provide critical insights for the development of novel therapeutic strategies targeting USP10.

Transcriptional level. Transcription is essential for gene expression and cellular function. As key regulatory molecules, transcription factors modulate gene expression by binding DNA sequences and influencing transcriptional activity through their effector domains. Dysregulation of transcription can alter gene expression patterns, which can aid in the onset and progression of various diseases. The transcriptional activity of USP10 is regulated by factors such as Yin Yang-1 (Yy1), c-Myc, FOXC1 and pleomorphic adenoma gene like-2 (PLAGL2). Yy1 downregulates USP10 transcription, aggravating pathological cardiac hypertrophy (95). Conversely, c-Myc induces USP10 transcription, which stabilizes p14ARF protein; USP10, in turn, deubiquitinates p14ARF, preventing its proteasome-dependent degradation and accelerating mouse embryonic fibroblast hyperproliferation (96). FOXC1 transcriptionally upregulates USP10 mRNA, thereby activating Wnt signaling and promoting PDAC progression (89). PLAGL2 enhances the transcription of the USP10 promoter by interacting with it, while USP10 deubiquitinates and stabilizes PLAGL2 protein, forming a positive feedback loop that mutually reinforces transcriptional activation (97).

Post-translation modification

Phosphorylation. USP10 activity is regulated in part through phosphorylation of its N-terminal domain. Yuan *et al* (34) demonstrated that, following DNA damage, ATM phosphorylates USP10 at Thr42 and Ser337, promoting its nuclear translocation. In the nucleus, the N-terminal region of USP10 interacts with p53 and prevents it from becoming ubiquitinated. Similarly, another study indicated that co-stimulation of B cells express BCR (a surface receptor for antigen) and Toll-like receptor (TLR)1/2 triggers AKT-dependent phosphorylation of USP10 at Thr674, leading to nuclear translocation and stabilization of AID (58). Under energy stress, AMP-activated protein kinase (AMPK) phosphorylates USP10 at Ser76, enhancing USP10-mediated deubiquitination of AMPK. In turn, USP10 promotes AMPK activity through K63-linked deubiquitination, establishing a positive feedback loop to respond to fluctuations in cellular energy metabolism (40). Likewise, it has been shown that activated AMPK phosphorylates USP10 at Ser76 to enhance deubiquitination and stability of the scaffold protein Axin1 (98). This phosphorylation also strengthens USP10/β-catenin interaction and supports β-catenin phase separation, thereby inhibiting tumor growth (98). Conversely, Sun *et al* (99) revealed that ERK phosphorylates USP10 at Ser236, which weakens the association of USP with zinc finger E-box binding homeobox 1 (ZEB1), enhancing ZEB1 protein stability and promoting colorectal cancer metastasis.

Histone methylation. Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the polycomb repressive complex 2 and a highly conserved histone methyltransferase. EZH2 modulates downstream gene expression by catalyzing trimethylation of lysine 27 on histone H3 (H3K27me3) (100). Lei *et al* (101) demonstrated that EZH2 modulates protein stability in malignant cells by recruiting USP7, thereby influencing neuronal gene expression. Huang *et al* (102) demonstrated that EZH2 promotes USP22 transcription by modulating H3K27me3 at the USP22 promoter, which in turn enhances programmed death-ligand 1 (PD-L1) protein stability. Recently, EZH2 was shown to suppress USP10 expression by increasing H3K27me3 at the USP10 promoter. This repression enhanced ubiquitin-mediated degradation of glutathione peroxidase 4, ultimately promoting ferroptosis in alveolar epithelial cells during sepsis (103).

Ubiquitination and PARylation. USP13 stabilizes USP10 by removing ubiquitin chains through its deubiquitinase activity, therefore averting proteasome-mediated destruction (68). Notably, Beclin1 can modulate the deubiquitination activity of both USP10 and USP13, controlling their protein stability (68). Mechanistically, Beclin1 functions as a scaffold within the Vps34 complex, maintaining the integrity and deubiquitinating capacity of USP10 and USP13. Notably, by

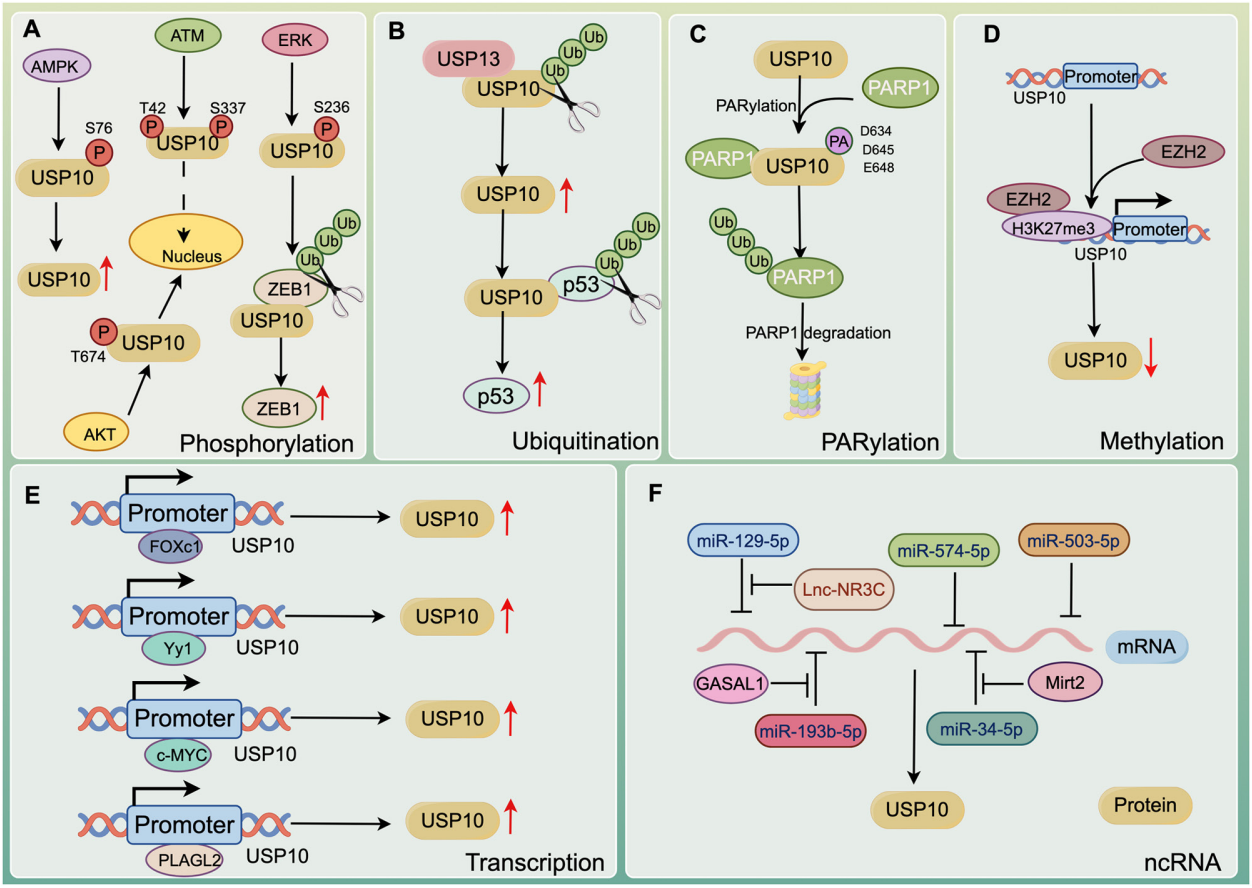

Figure 4. Regulation of USP10 expression. The multilayered regulatory pathways controlling USP10 at post-translational and transcriptional levels are presented. (A) Phosphorylation: USP10 is phosphorylated by AMPK and ATM in response to metabolic stress and DNA damage, respectively, promoting its stabilization and nuclear function. By contrast, AKT and ERK phosphorylate USP10 downstream of growth factor signaling, modulating its activity and substrate interactions. (B) Ubiquitination: USP10 protein stability is regulated by ubiquitination, leading to proteasomal degradation and maintaining appropriate intracellular USP10 levels. (C) PARylation: PARP1-mediated PARylation of USP10 occurs upon DNA damage and oxidative stress, facilitating its recruitment to chromatin and engagement in DNA damage response pathways. (D) Methylation: EZH2 represses USP10 expression through histone methylation at the USP10 promoter, establishing a transcriptionally repressive chromatin state. (E) Transcriptional regulation: USP10 transcription is directly regulated by ZEB1, FOXC1, YY1 and PLAGL2, which bind to its promoter and modulate gene expression in a context-dependent manner. (F) ncRNA regulation: ncRNAs regulate USP10 expression post-transcriptionally by controlling mRNA stability and translation efficiency. AMPK, AMP-activated protein kinase; ATM, ataxia telangiectasia mutated; AKT, protein kinase B; ZEB1, zinc finger E-box binding homeobox 1; USP10/13, ubiquitin-specific protease 10/13; ERK, extracellular signal-regulated kinase; PARP1, poly(ADP-ribose) polymerase 1; FOXc1, forkhead box C1; Yy1, Yin Yang-1; PLAGL2, pleomorphic adenoma gene like-2; EZH2, enhancer of zeste homolog 2; GASAL1, long non-coding RNA GASAL1; Mirt2, long non-coding RNAs Mirt2; P, phosphorylation; Ub, ubiquitination; PA, PARylation; mRNA, messenger RNA; ncRNA, non-coding RNA; miR, microRNA.

interacting with and stabilizing USP13, Beclin1 indirectly facilitates USP13-mediated deubiquitination of USP10, thereby contributing to maintaining USP10 stability (68). PARylation, a post-translational modification required for initiation of the DDR, also regulates USP10. PARP1, a key enzyme in the mammalian (ADP-ribosyl) transferase family, catalyzes PARylation (104). A recent study revealed that PARP1-mediated PARylation of USP10 at D634, D645 and E648 enhances its deubiquitination activity, thereby amplifying the DDR (39).

Non-coding RNAs (ncRNA). MicroRNAs (miRNA/miR) bind sequence-specifically to the 3'-untranslated region (3'-UTR) of target mRNAs, promoting degradation or preventing translation. For instance, Peng *et al* (105) identified USP10 as a direct target of miR-503-5p, which binds its conserved 3'-UTR region and suppresses both USP10 mRNA and protein expression. Similarly, Ma *et al* (106) reported that miR-574-5p upregulation reduces USP10 expression. Conversely, several ncRNAs, including long ncRNA (lncRNA)-NR3C (107), Mirt2 (108) and GASAL1 (109), have been shown to increase USP10 expression.

Together, these findings represent only part of the regulatory mechanisms governing USP10 (Table I). With further investigation, future studies are expected to integrate transcriptional, translational and post-translational layers to construct a more comprehensive network of USP10 regulation.

4. USP10 in human diseases

Due to its central role in regulating stress responses, genome stability, immune activation and protein homeostasis, dysregulation of USP10 has been associated with the pathogenesis of several human diseases. The present section highlights the major disease systems in which USP10 has demonstrated pathogenic relevance.

Table I. Modulation of USP10 expression.

Authors, year	Type	Modulator	Molecular mechanism	Cellular effect	(Refs.)
Li *et al*, 2025	Transcription	Yy1	Yy1 modulates USP10 transcription via directly binding to the promoter sequence	Increases USP10 transcription	(95)
Ko *et al*, 2018		c-Myc	c-Myc promotes p14AFR protein expression by inducing USP10 transcription	Increases USP10 transcription	(96)
Wang *et al*, 2024		FOXC1	FOXC1 and USP10 form a positive feedback loop, thus activating WNT signaling	Increases USP10 transcription	(89)
Wang *et al*, 2024		PLAGL2	PLAGL and USP10 form a signaling feedback loop	Increases USP10 transcription	(97)
Yuan *et al*, 2010	Phosphorylation	ATM	ATM phosphorylates Thr42 and Ser337 residues of USP10	Hinders USP10 nuclear export	(34)
Deng *et al*, 2016		AMPK	AMPK phosphorylates Ser76 residues of USP10	Enhances USP10 activity	(40)
Luo *et al*, 2022		AKT	AKM phosphorylates T674 residues of USP10	Regulates USP10 nuclear translocation	(58)
Wang *et al*, 2023		AMPK	AMPK phosphorylates Ser76 residues of USP10	Enhances USP10 activity	(98)
Sun *et al*, 2023		ERK	ERK phosphorylates Ser236 residues of USP10	Enhances the USP10-ZEB1 interaction	(99)
Liu *et al*, 2025	PARylation	PARP1	PARP1 PARylates D634, D645 and E648 residues of USP10	Increases USP10 expression	(39)
Liu *et al*, 2011	Ubiquitination	Usp13	USP13 mediated deubiquitination of USP10	Enhances stability of USP10	(68)
Dai *et al*, 2024	Methylation	EZH2	EZH2 promotes histone H3K27 modification of USP10 promoter	Reduces USP10 expression	(103)
Peng *et al*, 2025	ncRNA	miR-503-5p	miR-503-5p targets and downregulates USP10	Reduces USP10 translation	(105)
Ma *et al*, 2025		miR-574-5p	miR-574-5p targets USP10	Reduces USP10 expression	(106)
Pang *et al*, 2024		Lnc-NR3C	lnc-NR3C competitively binds miR-129-5p	Increases USP10 expression	(107)
Zhang *et al*, 2019		Mirt2	Mirt2 as the sponge of miR-34a-5p	Increases USP10 expression	(108)
Shen *et al*, 2022		GASAL1	GASAL1 could sponge miR-193b-5p	Increases USP10 expression	(109)

AMPK, AMP-activated protein kinase; ATM, ataxia telangiectasia mutated; AKT, protein kinase B; ZEB1, zinc finger E-box binding homeobox 1; USP10, ubiquitin-specific protease; ERK, extracellular signal-regulated kinase; PARP1, poly(ADP-ribose) polymerase 1; FOXC1, forkhead box C1; Yy1, Yin Yang-1; PLAGL2, pleomorphic adenoma gene like-2; EZH2, enhancer of zeste homolog 2; miR/miRNA, microRNA; ncRNA, non-coding RNA; GASAL1, long non-coding RNA (lncRNA) GASAL1; Mirt2, lncRNA Mirt2.

Cancer

USP10 in tumorigenesis and metastasis. Growing data suggest that dysregulation of USP10 is closely related to cancer initiation, cell proliferation and metastasis. Li *et al* (50) demonstrated that USP10 promotes CRC progression and tumor-associated macrophage polarization through deubiquitination of NLR family pyrin domain containing (NLRP)7. Similarly, USP10 stabilizes Musashi-2 via deubiquitination to enhance tumor proliferation in colon cancer (110). PLAGL2, a zinc finger transcription factor implicated in multiple cancers (111,112), is stabilized by USP10-mediated deubiquitination. Adrenergic signaling through the adrenergic β-receptor 2-c-Myc axis upregulates USP10, which stabilizes PLAGL2 and drives hepatocellular carcinoma (HCC) progression (97). In pancreatic cancer, Quan *et al* (41) reported that USP10 deubiquitinates phosphoglycerate kinase 1 (PGK1), enhancing its protein stability and promoting aerobic glycolysis. Kruppel-like factor (KLF)15 acts as a scaffold to improve USP-PGK1

interaction, further supporting proliferation and metastasis. Wang *et al* (113) showed that tribbles pseudokinase 3 binds USP10 to increase structure specific recognition protein 1 expression, promoting multiple myeloma (MM) progression. USP10 also deubiquitinates KLF4, and loss of USP10 downregulates KLF4 to facilitate lung tumorigenesis (114). Additionally, LINC00240 stabilizes DEAD-box helicase 21 (DDX21) and accelerates the development of gastric cancer (GC) by suppressing USP10-mediated deubiquitination of DDX21 (115).

USP10 further contributes to tumor proliferation by preventing degradation of key cell-cycle regulators such as c-Myc and cyclins D1/D3. For instance, USP10 antagonizes transient c-Myc activation through SIRT6 and TP53, suppressing cell-cycle progression, tumor growth and oncogenesis (116). SIRT6, a tumor suppressor, is stabilized by USP10-mediated deubiquitination. In HCT1 colon cancer cells, overexpression of either USP10 or SIRT6 decreases the proportion of cells in G_2/M phases while increasing the G_0/G_1 phase, with combined overexpression showing an enhanced effect (116). USP10 also stabilizes cyclin D1 (117) and cyclin D3 (118), promoting GBM and MM progression. Furthermore, USP10 increases TNF receptor superfamily member 10b stability to inhibit epithelial-mesenchymal transition (EMT) in GC (119), and stabilizes Yes1 associated transcriptional regulator (YAP1) to promote osteosarcoma metastasis and EMT (120).

As previously noted, USP10 regulates multiple signaling pathways, including Wnt, NF-κB and TGF-β. Wang *et al* (89) identified a positive feedback loop between USP10 and FOXC1, which activates Wnt signaling and drives PDAC malignancy. USP10 stabilizes K(lysine) acetyltransferase 8 (KAT8, also known as MOF) to epigenetically activate ANXA2/Wnt signaling, enhancing proliferation and metastasis in ESCC (121). USP10 also represses NF-κB activation by promoting monocyte chemotactic protein-1-induced protein-1-mediated deubiquitination of K63-linked linear ubiquitin chains on NF-κB essential modulator (122). By directly engaging with Smad4 and inhibiting its proteasomal degradation, USP10 facilitates HCC metastasis (86). Liu *et al* (123) demonstrated that USP10 suppresses YAP1 ubiquitination and degradation, promoting cysteine rich angiogenic inducer 61 (Cyr61) expression, immune evasion, tumor growth and metastasis. By contrast, USP10 can suppress HCC progression by inhibiting mTOR activation (124). A study also showed that circPOKE regulates USP10-mediated Snail deubiquitination, influencing breast cancer metastasis and stemness (125). In summary, USP10 is pivotal in modulating cell proliferation, metastasis and signaling across multiple cancers, including CRC, PDAC, GC, GBM, ESCC, HCC and breast cancer. Beyond promoting proliferation, USP10 also contributes to the maintenance of cancer stem cells (CSCs).

USP10 in cancer stemness and immune regulation. USP10 is identified as a CSC marker that facilitates the development and maintenance of CSCs by modulating the expression of stemness-related genes, including CD44, a non-kinase transmembrane glycoprotein intricately linked to CSC proliferation and tumor progression (126). USP10-mediated deubiquitination stabilizes CD44, enhancing breast cancer proliferation, stemness and metastasis (127). Additionally, Shi *et al* (128) reported that USP10 promotes CSC traits in head and neck squamous cell carcinoma by stabilizing bromodomain adjacent to zinc finger domain protein 1A. In CRC, USP10 drives CSCs and mediates 'super-competition' signaling to support tumor aggressiveness (129).

Growing data suggest that USPs are essential in immune regulation (28,130). For instance, USP8 is involved in T-cell growth, development and homeostasis (131), while USP22 stabilizes nuclear factor of activated T cells 2, a regulator of T-cell activation, thereby influencing IL-2 transcription and immune responses (132). USP2 interacts directly with PD-L1, removing K48-linked polyubiquitin chains to enhance PD-L1 expression in tumor cells. Loss of USP2 triggers endoplasmic reticulum-associated PD-L1 degradation, increases $CD8^+$ T-cell infiltration and reduces the immunosuppressive activity of myeloid-derived suppressor cells and regulatory T cells, thereby reshaping the tumor immune microenvironment (133).

USP10 contributes to immune evasion in multiple ways. It inhibits YAP1 ubiquitination and degradation, upregulates Cyr61 and promotes PDAC growth and metastasis (123). TANK, a TRAF family-related NF-κB activator, mediates USP10-dependent deubiquitination of TRAF6, suppressing NF-κB activation and IL-1R/TLR signaling (134). These pathways suggest that USP10 may influence tumor inflammation and immune responses. Emerging evidence also implicates USP10 in regulating the infiltration of diverse immune cells within malignancies, perhaps modulating the abundance of specific immune cell types (135). USP10 may also function as a regulator of PD-L1. It stabilizes PD-L1 by direct deubiquitination and indirectly via the USP10/ nuclear Dbf2-related 1/PD-L1 axis (136). In esophageal cancer, FOXP4-antisense 1 promotes $CD8^+$ T-cell exhaustion and immune escape by stabilizing PD-L1 through USP10 (137). Furthermore, USP10 inhibits autocrine motility factor receptor-mediated B7-H4 ubiquitination, stabilizing B7-H4 and suppressing tumor immune activity, which reduces the efficacy of SG-targeted therapies (138).

In conclusion, these data highlight USP10 as a key modulator of CSC maintenance and tumor immune regulation, although further studies are required to fully clarify its processes across different cancer contexts.

USP10 in cancer drug resistance. Beyond its role in tumor progression, USP10 contributes to cancer drug resistance, often by enhancing DNA damage repair. USP10 binds to XAB2 and removes K48-linked polyubiquitin chains at K593, thereby stabilizing XAB2. XAB2 subsequently binds to the ANXA2 promoter, upregulating ANXA2 transcription, facilitating DNA damage repair, alleviating oxaliplatin-induced DNA damage and boosting oxaliplatin resistance (38). Similarly, USP10 deubiquitinates and stabilizes ATM interactor (ATMIN), leading to its upregulation in nasopharyngeal carcinoma. ATMIN transcriptionally activates its downstream target lymphocyte-specific protein tyrosine kinase, promoting cell proliferation and docetaxel resistance (139). Another study revealed that DDB1 and CUL4-associated factor 7 acts as a scaffold to recruit USP10 to G3BP1, enhancing nasopharyngeal carcinoma chemoresistance and metastasis (140). USP10 also cooperates with protein phosphatase 1B (PPM1B) to regulate Y box binding protein 1 (YBX1)-mediated

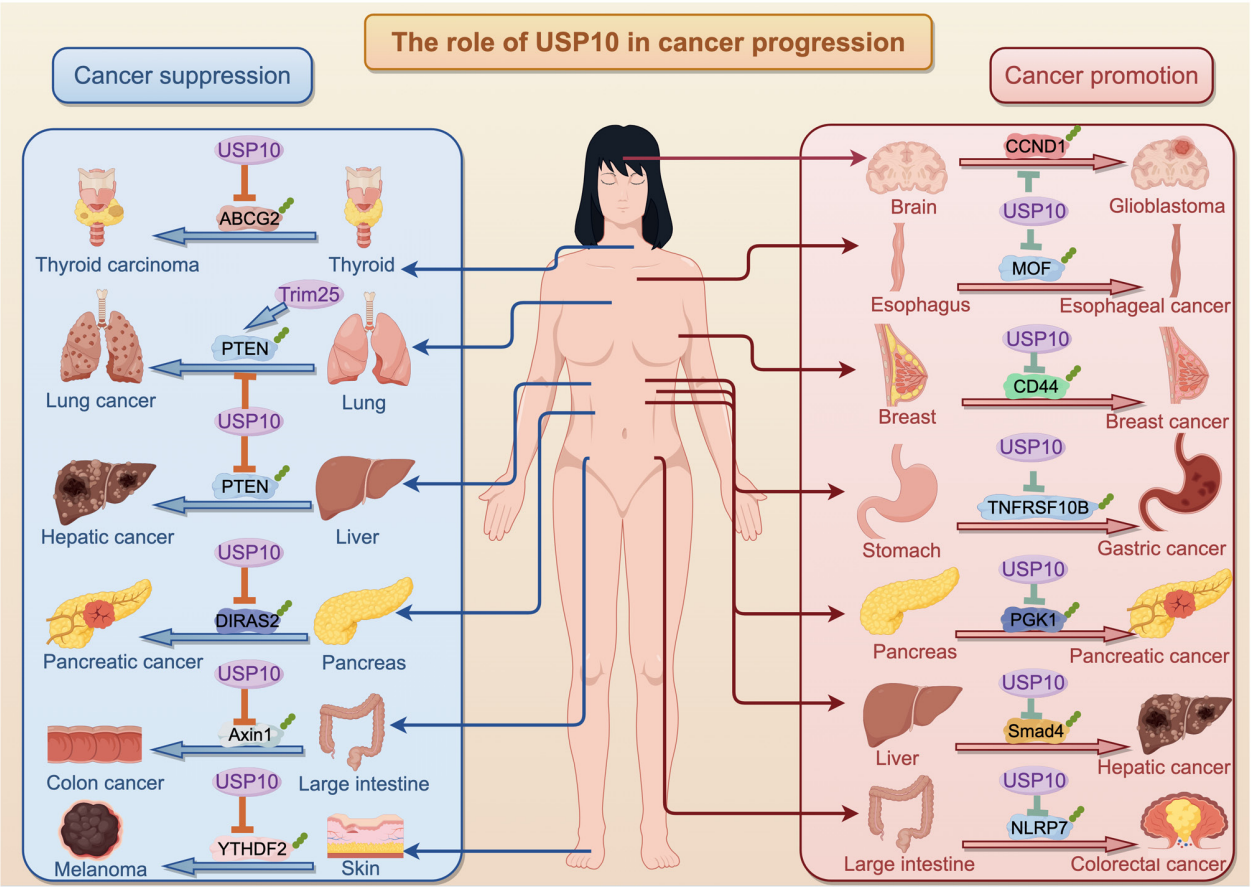

Figure 5. Dual role of USP10 in various cancer types. USP10 promotes glioblastoma, esophageal cancer, gastric cancer, hepatic cancer, colorectal cancer and breast cancer progression via regulating oncoprotein (such as CCND1, MOF and CD44) ubiquitination, meanwhile it also suppresses thyroid carcinoma, lung cancer, hepatic cancer, colon cancer and pancreatic cancer via regulating tumor suppressor protein (such as PTEN, Axin1 and DIRAS2) ubiquitination. ABCG2, adenosine triphosphate-binding cassette subfamily G member 2; CCND1, cyclin D1; PTEN, phosphatase and tensin homolog; DIRAS2, DIRAS family GTPase 2; Axin1; YTHDF2, YTH (YT521-B homology) domain 2; CCN1, cellular communication network factor 1; PGK1, phosphoglycerate kinase 1; NLRP7, NACHT, LRR and PYD domain-containing protein 7; MOF, K(lysine) acetyltransferase 8; Trim25, tripartite motif-containing 25; TNFRSF10B, TNF receptor superfamily member 10b; USP, ubiquitin-specific protease; Smad4, SMAD family member 4.

anti-apoptotic signaling. PPM1B directly interacts with YBX1, inducing dephosphorylation at serine 314, which affects USP10-mediated YBX1 deubiquitination, reduces YBX1 protein levels and modulates apoptosis and oxaliplatin resistance in GC cells (141).

Furthermore, Notch1 degradation-associated regulatory polypeptide (N1DARP) exerts tumor-suppressive and chemosensitizing effects by modulating the USP10-Notch1 oncogenic signaling axis, suggesting a promising therapeutic strategy targeting the N1DARP-Notch1 intracellular domain (N1ICD) interaction in Notch1-activated pancreatic cancer (142). In ESCC, USP10 is essential for cisplatin resistance and migration through deubiquitination and stabilization of integrin β1/YAP, highlighting USP10 inhibition as a potential therapeutic approach (143). Therefore, these studies underscore that USP10 is pivotal in tumor invasion, metastasis, immunological modulation and chemoresistance. Nevertheless, the detailed molecular mechanisms underlying its diverse functions remain to be fully elucidated.

USP10 in cancer suppression. In cancer, USP10 primarily acts as an oncogene, while it can also function as a tumor suppressor (Fig. 5). Lu *et al* (124) found that the expression of USP10 was markedly downregulated in HCC tumor tissues compared with adjacent non-cancer tissues, and in several independent cohorts, low USP10 levels were associated with low patient survival. Mechanistically, USP10 stabilizes AMPKα and phosphatase and tensin homolog (PTEN) in HCC cells, thereby negatively regulating mTORC1 activation and AKT phosphorylation, ultimately inhibiting HCC progression. In addition, this study also analyzed the correlation between the high and low expression of USP10 and hepatitis B/C, TNM stage, tumor size and Barcelona-Clinic Liver Cancer (BCLC) stage, and found that only tumor size and BCLC staging were associated with USP10 expression (124). Additionally, as mentioned above, elevated USP10 expression has been observed in metastatic or aggressive HCC, consistent with experimental findings supporting a pro-metastatic role through the stabilization of Smad4 (86). Regrettably, current cohorts do not stratify USP10 expression by HCC etiology [HBV/HCV/non-alcoholic steatohepatitis (NASH)] or by molecular subtype, and no published study has systematically evaluated USP10 across distinct TNM stages within defined etiologic subgroups, which may be a novel direction for future research. Similarly, USP10 activates PTEN by preventing tripartite motif-containing 25-mediated K63-linked polyubiquitination, suppressing the AKT/mTOR signaling pathway

and inhibiting proliferation in NSCLC (144). Sun *et al* (145) further demonstrated that USP10 suppresses lung cancer cell growth and invasion by upregulating PTEN. In the thyroid cancer cell line FTC133, low USP10 expression was observed; USP10 overexpression activated PTEN, repressed PI3K/AKT signaling and downregulated ABCG2, thereby suppressing doxorubicin-resistant thyroid cancer invasion, migration and EMT (92).

Similarly, in CRC cells, USP10 suppresses metastasis by stabilizing the zinc finger E-box binding homeobox 1 protein (99). Luo *et al* (146) showed that USP10 deubiquitinates and stabilizes YTH N6-methyladenosine RNA binding protein F2 (YTHDF2), inhibiting melanoma proliferation and migration. Disruption of the USP10-YTHDF2 interaction by lncRNA JPX promotes YTHDF2 degradation, stabilizes BMP2 mRNA, activates AKT phosphorylation and accelerates melanoma progression (146). Furthermore, N1DARP exerts tumor-suppressive and chemosensitizing effects by modulating USP10-Notch1 oncogenic signaling, suggesting a potential treatment approach aimed at the N1DARP-N1ICD interaction in Notch1-activated pancreatic cancer (142). In PC cells, Chen *et al* (147) indicated that USP10 regulated the stability of DIRAS family GTPase 2 through deubiquitylation, suppressing PC growth. In CRC, USP10 suppresses tumor growth primarily by facilitating phase separation, and its expression is associated with clinical Wnt/β-catenin signaling levels (148).

Overall, these results indicate that USP10 can act as a context-dependent tumor suppressor, regulating multiple pathways including PTEN, AKT/mTOR, Notch1 and Wnt/β-catenin to inhibit tumor growth, invasion, metastasis and drug resistance.

Neuroinflammation and neurodegenerative diseases. In ischemic stroke, vagus nerve stimulation alleviates neurological deficits, neuroinflammation and glial activation by repressing the NF-κB signaling pathway, with USP10 likely playing a key role in this process (88). Additionally, USP10 suppresses transforming growth factor β-activated kinase 1 (TAK1) signaling, reducing inflammation and apoptosis, thereby mitigating brain ischemic injury (74).

In neurodegenerative disorders such as Alzheimer's disease (AD), characterized by tau protein aggregation in neurons, USP10 participates in tau pathology. The RNA-binding protein TIA1 initiates tau aggregation by promoting SG formation. In the early stages of AD and Parkinson's disease (PD), SG formation is common. Piatnitskaia *et al* (149) demonstrated that USP10 is essential for T-cell intracellular antigen 1 (TIA1)/tau-positive SG assembly, and that catalytically inactive USP10 can still promote tau/TIA1/USP10-positive SG formation, indicating a deubiquitinase-independent, protein-interaction-driven role in SG dynamics. By contrast, Wei *et al* (26) showed that USP10 directly deubiquitinates tau, reducing its ubiquitination and turnover and thereby promoting aggregation. Additionally, Cai *et al* (150) suggested that USP10 may also interact with β-site amyloid precursor protein cleaving enzyme 1, affecting hippocampal volume and contributing to AD pathogenesis. In PD, α-synuclein is a major pathogenic factor. Anisimov *et al* (151) found that USP10 inhibits chaperone-mediated autophagy, suppressing α-synuclein degradation and slowing PD progression.

In amyotrophic lateral sclerosis (ALS), USP10 facilitates the clearance of TAR DNA-binding protein 43 (TDP)-43/TDP-35-positive SGs while promoting proper aggregate formation, thereby reducing cytoplasmic TDP-43/TDP-35 mis-accumulation and neuronal toxicity (152). Pang *et al* (107) further demonstrated that the lncRNA NR3C2-8:1 upregulates USP10 and activates p53, promoting p53-mediated apoptosis in ALS. Conversely, lnc-NR3C knockdown suppresses the activation of p53 that is mediated by USP10, therefore shielding cells from oxidative damage.

Organ dysfunction and fibrosis. Beyond its roles in cancer, USP10 also serves critical roles in cardiovascular, renal, hepatic and pulmonary diseases (Fig. 6). This section will examine the mechanisms and functions of USP10 in these non-cancer pathologies.

Cardiovascular diseases. Recently, growing findings have revealed that USP10 serves critical roles in various cardiovascular pathologies, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), ischemic heart disease and vascular remodeling. In HCM, USP10 expression is upregulated and correlates with impaired cardiac contractile function. Mechanistically, USP10 deubiquitinates Sirt6, thereby repressing the Akt signaling pathway and attenuating cardiomyocyte hypertrophy (153). Li *et al* (95) further confirmed that USP10 exerts protective effects in pressure overload-induced pathological hypertrophy. Specifically, USP10 interacts with cytoplasmic Mfn2 via His-679 in its UCH domain, removing K11/K48-linked ubiquitin chains to prevent proteasomal degradation, thereby maintaining mitochondrial function and cellular homeostasis.

In diabetic cardiomyopathy, USP10 activates Notch1, protecting against myocardial injury in type 2 diabetic mice (154). In models of hypoxia/reoxygenation, USP10 protects H_9C_2 cells from apoptosis and oxidative stress by activating the Hippo/YAP pathway, while FOXO4 acts as a negative transcriptional regulator of USP10 to suppress Hippo/YAP activation (91). By contrast, in DCM, USP10 promotes endothelial-to-mesenchymal transition (EndMT) via SMAD4/TGF-β1 signaling, exacerbating disease progression, whereas EGF like and discoidin domains 3 deficiency attenuates EndMT by inhibiting USP10-dependent Smad4 deubiquitination (155). In ischemic cardiomyopathy, USP10 in cardiac fibroblasts deubiquitinates SMAD4 to activate TGF-β/SMAD4 signaling, promoting cardiac fibrosis (156). Additionally, USP10 expression is upregulated in doxorubicin-treated mouse hearts, H9C2 and HL-1 cells when Ca^{2+}/calmodulin-dependent protein kinase is inhibited; this protective regulation against apoptosis and ubiquitination is blocked by the USP10 inhibitor Spautin-1 (157). Heat shock protein A12A acts as a scaffold for USP10 and p53, promoting USP10-mediated deubiquitination of p53, stabilizing p53 and inhibiting p53-mediated glycolysis, thereby alleviating cardiac fibrosis (158).

USP10 also regulates vascular signaling pathways beyond the heart. It deubiquitinates and stabilizes the transcriptional coactivator Yorkie, thereby modulating the Hippo pathway (90). In retinal endothelial cells, USP10 stabilizes the intracellular domain of Notch1, regulating Notch signaling and having an effect on retinal angiogenesis and vascular homeostasis (85). In pulmonary vascular cells, USP10 inhibits BUB3 mitotic

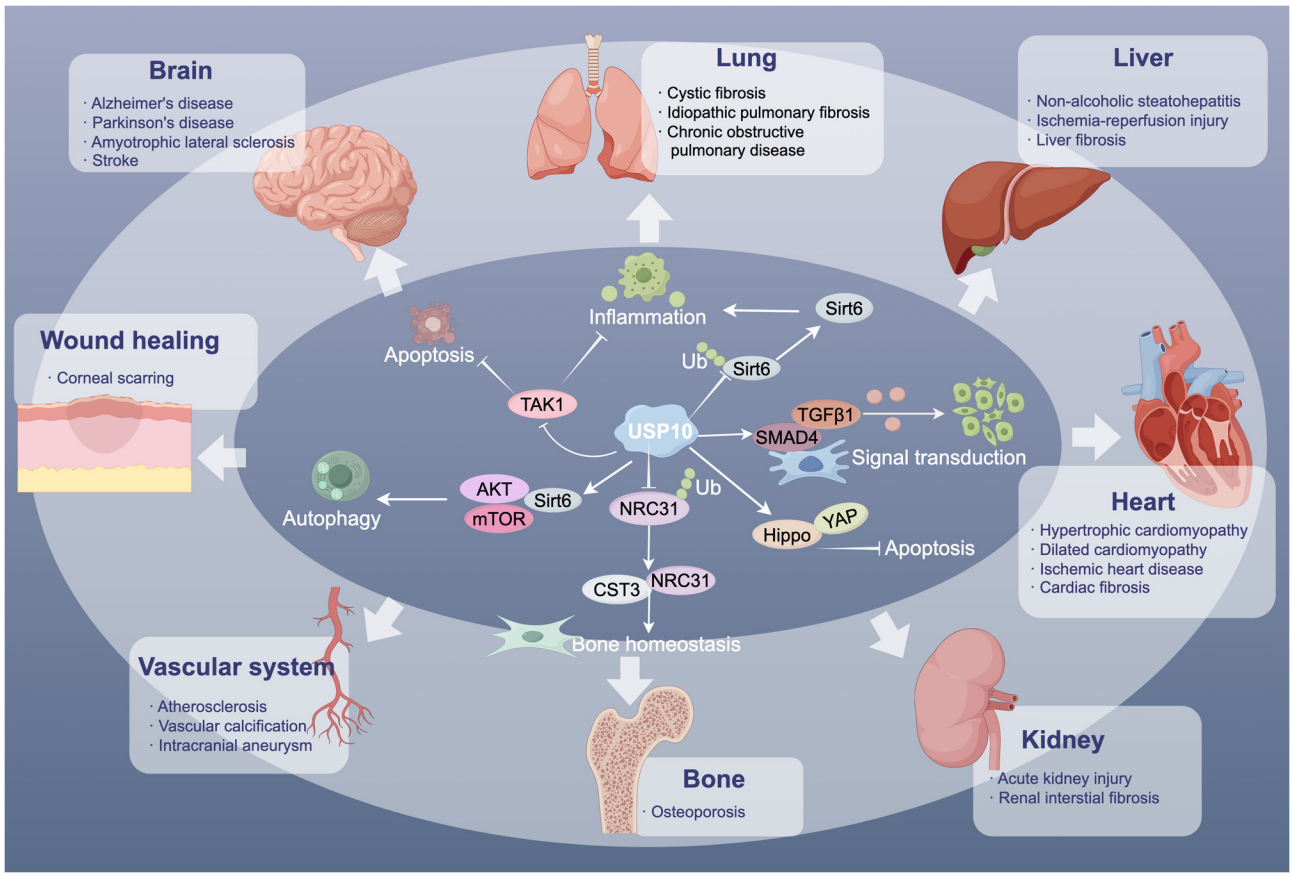

Figure 6. Overview of USP10 in non-cancer diseases. The progression of multiple diseases was found to be associated with USP10, including those of the cardiovascular system, bone and kidney. Mechanistically, USP10 regulates key cellular processes such as inflammation, apoptosis, autophagy, signal transduction and bone homeostasis, through modulation of TAK1, Sirt6/AKT/mTOR, TGF-β/SMAD4, Hippo/YAP and NRC31-associated pathways. Dysregulation of USP10-mediated deubiquitination contributes to pathological processes across multiple tissues, including the brain, lung, liver, heart, kidney, vasculature, bone and wound-healing tissues. Arrows denote regulatory relationships. Ub, ubiquitination; USP, ubiquitin-specific protease; TAK1, transforming growth factor β-activated kinase 1; AKT, protein kinase B; CST3, controlling cystatin-3; NR3C1, nuclear receptor subfamily 3 group C member 1; TGF-β, transforming growth factor β.

checkpoint protein (BUB3) ubiquitination, increasing BUB3 stability, which drives cell growth and survival via non-canonical Hippo/mammalian Ste20-like kinases signaling involving BUB3 and FOXO (159). Vascular smooth muscle cells (VSMCs) are also influenced by USP10. In ligated carotid arteries, USP10 expression is elevated, stabilizing Skp2 and promoting VSMC proliferation and migration, thus exacerbating neointimal formation (160). In diabetes-associated vascular calcification and atherosclerosis, USP10 mediates AMPKα ubiquitination, increasing Thr172 phosphorylation and aggravating vascular calcification (161). Recently, a study revealed that lncRNAs interact with USP10 and KLF4 to enhance NLRP3 transcription, driving pyroptosis in human brain VSMCs and contributing to intracranial aneurysm progression (162).

Hepatic diseases. In an animal model of hepatic I/R injury, Zhou *et al* (163) demonstrated that USP10 alleviates liver damage by inhibiting TAK1-JNK/p38 signaling, which in turn suppresses hepatocyte inflammation and apoptosis. Overexpression of USP10 effectively reduces hepatic I/R injury by mitigating hepatic inflammatory responses and apoptosis. In NASH models, USP10 deubiquitinates and stabilizes Sirt6, which suppresses hepatic steatosis, insulin resistance and inflammation (75). USP10 also improves liver lipid metabolism by restoring autophagic activity (164). In HepG2 cells, USP10 regulates the JNK1/tuberous sclerosis complex signaling pathway to promote autophagic flux, thereby alleviating palmitate-induced steatosis (165). Furthermore, Tian *et al* (166) reported that USP10 deubiquitinates and stabilizes KLF4, modulating NF-κB/STAT6 signaling and matrix metalloproteinase 12 transcription, which influences macrophage polarization and inflammatory responses, ultimately attenuating liver fibrosis. These findings suggest that USP10, which mainly regulates inflammation, apoptosis, autophagy and macrophage-mediated fibrotic responses, may be a valuable therapeutic target in liver diseases.

Renal diseases. Renal interstitial fibrosis is a major determinant of chronic kidney disease progression, with renal tubular epithelial cells serving as key drivers of this pathological process. Liu *et al* (167) reported that USP10 facilitates renal interstitial fibrosis by deubiquitinating and stabilizing p53, which enhances its nuclear translocation and upregulates p21 expression, ultimately driving fibrotic progression. Knockout of USP10 or treatment with Spautin-1, an inhibitor of USP10 deubiquitinase activity, markedly reduces fibronectin expression and ameliorates TGF-β1-induced tubular epithelial cell dedifferentiation (167). USP10 also deubiquitinates and stabilizes FOXQ1, which exerts protective effects

against inflammation and apoptosis in sepsis-associated acute kidney injury (AKI) via the cAMP response element binding 5/NF-κB axis (168). Additionally, PR/SET domain 16 attenuates rhabdomyolysis-induced AKI by upregulating USP10 to inhibit ferroptosis (169). Similarly, USP10 modulates Sirt6-mediated Nrf2/antioxidant response element signaling, thereby alleviating sepsis-induced AKI (170).

Pulmonary diseases. Idiopathic pulmonary fibrosis is a progressive pulmonary disorder marked by fibroblast activation and collagen accumulation, with limited effective therapeutic interventions. Mao *et al* (171) reported that USP10 was markedly downregulated in bleomycin-induced pulmonary fibroblasts. Overexpression of USP10 mitigates lung injury and reduces collagen deposition. Mechanistically, USP10 integrates with Sirt6 to promote Sirt6/AKT/mTOR-mediated autophagy, thereby alleviating lung fibrosis.

Cystic fibrosis transmembrane conductance regulator (CFTR) is a cyclic AMP-regulated chloride channel critical for regulating airway surface liquid volume, facilitating mucociliary clearance and pathogen elimination. USP10 has been shown to regulate CFTR deubiquitination, affecting CFTR endocytic recycling in human airway epithelial cells (172,173). Cif (PA2934), a bacterial toxin secreted by *Pseudomonas aeruginosa* in outer membrane vesicles, reduces CFTR-mediated chloride secretion, which is essential for mucociliary clearance (174). Bomberger *et al* (175) demonstrated that Cif enhanced the interaction between G3BP1 and USP10, inhibiting USP10-mediated CFTR deubiquitination and increasing CFTR lysosomal degradation. These studies suggest that USP10 exerts a dual effect in lung disease, both by modulating autophagy in fibrotic processes and by regulating CFTR stability to maintain airway epithelial function.

Other diseases. USP10 has been shown to promote fibrotic wound healing by regulating integrin β1 and β5 (176). Conversely, USP10 overexpression can block TGF-β signaling or αv integrins on the cell surface, preventing or reducing the expression of fibrotic markers (176). In injured corneal fibroblasts, Boumil *et al* (177) demonstrated that USP10 knockdown can prevent corneal scarring. Beyond wound healing, USP10 exerts an important function in viral infection. Kaposi's sarcoma-related herpesvirus encodes viral interferon regulatory factor 1 (vIRF1), which undergoes lysine acetylation necessary to effectively inhibit IFN-β production and antiviral signaling. vIRF1 blocks the interaction between SIRT6 and USP10, resulting in vIRF1 degradation via the ubiquitin-proteasome pathway and promoting its own acetylation. Notably, vIRF1 acetylation is required for its ability to block IRF3-CREB-binding protein/p300 recruitment and suppress the stimulator of IFN-dependent genes DNA-sensing pathway (178). These results point to USP10 as a crucial modulator of tissue repair and viral immune evasion, suggesting potential therapeutic applications in fibrosis and viral infections.

5. Therapeutic application

Over the past decades, numerous small-molecule inhibitors that target DUBs have been developed and tested in preclinical studies, showing notable therapeutic potential, particularly in oncology (179,180). As previously discussed, USP10 is markedly upregulated in various malignancies and is associated with poor survival outcomes, making it a potential target for oncological treatment. Other USP10 inhibitors have recently been developed for human cancers, including Spautin-1, P22077, HBX19818, Wu-5 and D1.

Spautin-1 is a small-molecule inhibitor non-selectively targeting USP10 and USP13, which was reported by Liu *et al* (68) in 2011. Furthermore, Liu *et al* (68) also confirmed that Spautin-1 had no significant inhibitory effect on USP14 and CYLD. Notably, the impact of other DUBs (such as USP7) has not been systematically evaluated, which may cause the risk of off-target effects. A recent study showed that Spautin-1 can attenuate GBM progression by independently modulating RAF-ERK-mediated glycolysis and SKP2 (181). Similarly, it also inhibits EGFR phosphorylation and downstream signaling, suppressing prostate cancer progression (182). Furthermore, in combination with the chemotherapeutic agent cisplatin, Spautin-1 notably enhances antitumor activity and reduces osteosarcoma development (36). Of note, a recent study indicated that Spautin-1 promotes mitophagy via the PTEN induced kinase 1-parkin RBR E3 ubiquitin protein ligase pathway, improving associative learning in an AD *C. elegans* model (183).

Lu *et al* (184) found D1 was the optimal inhibitor of USP10 through dynamic simulation, compound library screening and molecular docking. Further study showed that the binding of D1 to USP10 is highly specific, which mainly depends on the allosteric hydrophobic structure adjacent to USP10 catalytic domain. Furthermore, the study showed that D1 barely inhibited USP7 activity even at concentrations up to 10 μM. D1 is a promising tool for USP10-positive HCC therapy, highlighting its utility in dissecting USP10's complex functions. Mechanistically, D1 inhibits USP10, leading to elevated ubiquitination of YAP protein, ultimately resulting in tumor cell cycle arrest at the S phase (184). Notably, D1 (USP10 IN-1) has been prepared in DMSO, which may limit its clinical transformation.

Other inhibitors include Ly-2, a high-affinity USP10 inhibitor that promotes apoptosis through cyclin-dependent kinase 4 downregulation in HCC. A study by Lu *et al* (185) revealed that Ly-2 is the first USP10 inhibitor to achieve nanomolar-level binding affinity in cells and *in vitro*. In this study, a Chai-1 model and sites mutation experiment confirmed that Ly2 binds to USP10 through the interaction between Ly-2 with Phe629 and Thr630. Compared with D1, Ly-2 showed notable affinity. Regrettably, the selectivity of Ly-2 for other DUBs was not evaluated; therefore, its specificity remains to be determined. Weisberg *et al* (186) found that HBX19818 and P22077 could inhibit USP10 (IC_{50}=6 μM), but also inhibit USP7 (IC_{50}=10 μM). In patient-derived xenograft models, P22077 exhibits selective antiproliferative effects against mutant FMS-like tyrosine kinase-3 (FLT3). Wu-5, another novel USP10 inhibitor, shows high selectivity for USP10. Yu *et al* (187) demonstrated that Wu-5 targets FLT3 and AMPKα pathways to overcome FLT3 inhibitor resistance and synergistically enhance the anti-AML effects of crenolanib *in vitro*. Furthermore, the study confirmed that Wu-5 inhibited the binding of HA-Ub-VS to USP10 but not to USP5 through DUB labeling. These findings indicate that Wu-5 directly interacts with USP10 *in vitro*. Notably, this study did not carry

Table II. USP10 inhibitors as potential target drugs.

Authors, year	Inhibitors	Target	Selectivity	Diseases	Mechanism	(Refs.)
Feng *et al*, 2024	Spautin-1	USP10/13	Non-selective	OS	Decreases autophagy levels and increases p62, thus inhibits OS growth *in vitro* and *in vivo*	(36)
Kona *et al*, 2024		USP10/13	Non-selective	GBM	Regulates RAF-ERK mediated glycolysis and SKP2, attenuating the progression of glioblastoma *in vitro* and *in vivo*	(181)
Liao *et al*, 2019		USP10/13	Non-selective	PCa	Inhibits EGFR phosphorylation and reduces GLUT1 expression, markedly triggers cell death under lack of glucose, suppressing Pca proliferation *in vitro* and *in vivo*	(182)
Ma *et al*, 2025	Melatonin	USP10	Not studied yet	ESCC	Inhibits the formation of ESSC tumors by suppressing the USP10-maintained HDAC7 protein stability and mitigating the HDAC7/β-catenin/c-Myc positive feedback loop	(54)
Sun *et al*, 2021	AVT	USP10	Not studied yet	GBM	Inhibits USP10 mediated deubiquitination on CCND1	(117)
Lu *et al*, 2024	D1	USP10	Highly selective	HCC	Facilitates the degradation of YAP, triggers the downregulation of p53 and its downstream protein p21 *in vitro* and *in vivo*	(184)
Lu *et al*, 2025	Ly-2	USP10	Not studied yet	HCC	Prevents the progression of HCC by blocking the proteasomal degradation of downstream proteins YAP and p53 *in vitro* and *in vivo*	(185)
Weisberg *et al*, 2017	P22077, HBX19818	USP7/10	Non-selective	ALM	Promotes degradation of FLT3-ITD *in vitro* and *in vivo*	(186)
Yu *et al*, 2021	Wu-5	USP10	Highly selective	AML	Targets FLT3 and AMPKα pathway *in vitro*	(187)
Han *et al*, 2025	Ginkgolic acid	USP10	Not studied yet	HCC	Inhibits the deubiquitinase activity of USP10	(188)
Cao *et al*, 2023	F806	USP10	Not studied yet	ESCC	Targets USP10 and promotes ANLN degradation	(189)
Ge *et al*, 2025	Acacetin	USP10	Not studied yet	Cardiac hypertrophy	Downregulates USP10 protein expression	(190)
Liu *et al*, 2022	Limonin	USP10	Not studied yet	Cardiac hypertrophy	Activates USP10, inhibits the degradation of SIRT6	(191)
Li *et al*, 2024	TSG	USP10	Not studied yet	Cerebral I/R injury	Upregulates USP10 and enhances YBX1	(192)

AVT, acevaltrate; ANLN, anilin; CCND1, cyclin D1; ESCC, esophageal squamous cell carcinoma; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; Pca, prostate cancer; GBM, glioblastoma; GLUT1, glucose transporter 1; HCC, hepatocellular carcinoma; TSG, tetrahydroxy stilbene glucoside; OS, osteosarcoma; USP10/13, ubiquitin-specific protease 10/13; YBX1, Y box binding protein 1.

out *in vivo* experiments, and its toxic effects (such as hepatoxicity) need to be further clarified.

Several natural compounds have also been identified to modulate USP10, offering alternative therapeutic strategies. For instance, ginkgolic acid stabilizes YAP1 via USP10, enhancing YAP1/TEA domain transcription factor 4-mediated transcription of prolyl 4-hydroxylase subunit alpha 1 and suppressing HCC progression (188). The macrolide

compound FW-04-806 (F806), with potential against ESCC, targets USP10 to promote ANLN degradation and inhibit mitosis (189). Acevaltrate inhibits USP10-mediated cyclin D (CCND1) demethylation, inducing CCND1 degradation and suppressing GBM progression (117). Acacetin enhances cardiac remodeling by inhibiting USP10-mediated Beclin1 ubiquitination and autophagy in cardiomyocytes (190), whereas limonin activates USP10-mediated SIRT6 ubiquitination and degradation, offering a potential target for cardiac hypertrophy (191). Tetrahydroxy stilbene glucoside promotes USP10-mediated YBX1 stabilization, enhancing mitophagy and alleviating neuronal injury after cerebral I/R (192). Additionally, melatonin suppresses ESCC proliferation by attenuating the histone deacetylase HDAC7/β-catenin/c-Myc positive feedback loop and reducing USP10-stabilized HDAC7 protein (54). Notably, whether these natural compounds have selective inhibitory effects on USP10 has not been studied, yet.

The development of selective USP10 inhibitors remains challenging owing to the high structural conservation of catalytic domains across the USP family. Most compounds reported to modulate USP10 activity are therefore regarded as broad-spectrum USP inhibitors or indirect regulators. Despite the challenges in DUB inhibitor development, two DUB-targeting small molecules, VLX1570 and KSQ-4279, have been advanced to phase I clinical trials for refractory MM (NCT02372240 and NCT05240898) (193,194). Collectively, these findings underscore the therapeutic promise of DUB inhibitors, particularly USP10-targeted agents, in treating cancer and other diseases (Table II).

6. Conclusions and future perspectives

USP10, a multifunctional deubiquitinase, participates in a wide range of physiological processes, including DNA damage repair, immune and inflammatory regulation, environmental adaptation and autophagy. Its ability to modulate diverse substrates, such as p53, AMPK, Beclin1 and ATM, highlights its critical role as a dynamic regulator of cellular stress responses. Furthermore, USP10 acts as a pivotal node in multiple signaling pathways, contributing to both tumor progression and suppression. A broad spectrum of diseases, including cancer, neurodegenerative and infectious diseases and organ fibrosis, have been linked to USP10 dysregulation.

Decades of research have driven the development of numerous USP10-targeting inhibitors. As a result of the notable therapeutic potential that has been established in preclinical research conducted on illness models, there is a rising interest in techniques that target USP10. Nevertheless, the context-dependent functions of USP10, particularly its dual roles in tumor promotion and suppression, necessitate careful consideration of disease states and compensatory signaling mechanisms. Furthermore, for a specific cancer, the association between USP10 and the etiology should be further clarified, which may be beneficial to cancer prevention and diagnosis. At present, numerous inhibitors targeting DUBs are still in preclinical research, while there is a lack of *in vivo* experiments, and the evaluation of the toxic and side effects of inhibitors is still lacking. Broad USP10 inhibition may be beneficial in certain cancers or fibrotic conditions but could be detrimental in scenarios where USP10 supports genome integrity or immune defense. Several key challenges must be addressed to translate USP10-targeted therapies into clinical practice: i) USP10 shares high structural similarity with other USPs, particularly USP13. Dual inhibition may confound mechanistic interpretation and therapeutic outcomes. Developing highly selective USP10 inhibitors remains a priority, necessitating further structural and mechanistic studies to map its molecular interactions comprehensively. Notably, there are no reports on the differences between USP10 and USP13 in catalytic cleft, thumb-finger interface and ubiquitin binding surface; therefore, further research should highlight these differences so that specific USP10 inhibitors are designed. While high-resolution experimental structures of full-length USP10 or its catalytic domain remain inaccessible, recent advances in structural modeling, including AlphaFold-derived predictions, may provide useful help for the structural elucidation of USP10 (195). These differences may form unique inhibitor-binding pockets, offering an opportunity for structure-guided development of next-generation USP10-selective inhibitors; ii) embedded within complex signaling networks, USP10 inhibition could trigger compensatory upregulation of other DUBs or pathway rewiring, potentially reducing efficacy or promoting resistance; iii) current inhibitors, such as Spautin-1, exhibit moderate potency, suboptimal pharmacokinetics and poor tissue distribution. Optimizing drug delivery, bioavailability and metabolic stability is essential; and iv) the cell-type specificity of USP10 across disease contexts is still unclear.

Future directions should focus on developing highly selective and potent USP10 inhibitors, elucidating its substrate landscape and interactions in specific disease contexts, and integrating USP10 modulation into rational combination therapies. For instance, pairing USP10 inhibitors with chemotherapy, immunotherapy or targeted agents may enhance antitumor efficacy and overcome compensatory resistance mechanisms. Additionally, leveraging structural biology, single-cell proteomics and chemical biology approaches will be crucial for fully delineating regulatory complexity of USP10 and providing a robust foundation for drug discovery and clinical translation.

Acknowledgements

Figs. 4-6 were created by FigDraw (https://www. figdraw.com).

Funding

This work was supported by Hubei Chen Xiaoping Science and Technology Development Foundation (grant no. CXPJJH122011-011) and the Wu JiePing Medical Foundation (grant no. 320.6750.2023-18-21).

Availability of data and materials

Not applicable.

Authors' contributions

LZ was involved in literature search, visualization and writing-original draft. HS provided resources and supervision

and performed visualization. ZiW was involved in visualization and software. ZhW conceptualized the study and provided resources. QM performed project administration and review & editing. YL provided supervision, acquired funding and performed review & editing. Data authentication is not applicable. All authors have read and approved the final manuscript.

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.

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