EBM Experimental Biology and Medicine

TYPE Review
PUBLISHED 20 November 2026
DOI 10.3389/ebm.2026.11322

Check for updates

OPEN ACCESS

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RECEIVED 03 August 2026
REVISED 07 November 2026
ACCEPTED 10 November 2026
PUBLISHED 20 November 2026

CITATION
Shaik MA, Banerjee A and Bernstein AM (2026) Ubiquitin-specific peptidase 10 as a context-dependent deubiquitination hub: integrating stress adaptation, disease progression, and therapeutic opportunities.
Exp. Biol. Med. 251:11322.
doi: 10.3389/ebm.2026.11322

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Ubiquitin-specific peptidase 10 as a context-dependent deubiquitination hub: integrating stress adaptation, disease progression, and therapeutic opportunities

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Abstract

Ubiquitination is a reversible post-translational modification that regulates protein stability, localization, and signaling, while deubiquitinases provide dynamic control over ubiquitin-dependent protein fate. Among these enzymes, ubiquitin-specific peptidase 10 (USP10) has emerged as a highly context-dependent regulator of cellular homeostasis and disease. USP10 influences diverse biological processes, including tumor progression, fibrotic remodeling, mechanotransduction, mitochondrial quality control, metabolic adaptation, and cellular stress responses. Its biological effects are often divergent: in some settings, USP10 supports protective pathways by stabilizing wild-type p53, promoting AMPK-dependent metabolic checkpoints, preserving mitochondrial integrity, and enhancing stress adaptation. In chronic disease contexts it drives pathology by stabilizing oncogenic or profibrotic substrates, including mutant p53, β-catenin, YAP/TAZ, EIF4G1, integrins, and SMAD4. In chronic inflammatory microenvironments, USP10 reinforces disease-promoting signaling through the NEMO/NF-κB and S100A9-SYK-NLRP3 inflammasome axes, increasing inflammatory mediators such as TNF-α, IL-6, CCL2, S100A9, caspase-1/GSDMD, ROS, and profibrotic TGF-β/CTGF pathways. This review synthesizes the dual and context-specific functions of USP10 across cancer, fibrosis, mitochondrial dysfunction, and tissue injury. Rather than functioning as an intrinsically protective or pathogenic enzyme, USP10 acts as a molecular switch whose output is determined by substrate availability, interacting partners, subcellular localization, disease stage, and the surrounding signaling environment. Because accumulating evidence implicates USP10 as a driver of pathology in multiple chronic disease settings, we also examined emerging therapeutic strategies to inhibit USP10 activity, including small-molecule inhibitors, RNA interference approaches, and substrate-selective disruptors. Understanding the context-dependent biology of USP10 will be essential for developing therapeutic strategies that suppress its disease-promoting functions while preserving or enhancing its protective roles.

KEYWORDS
cellular stress response, deubiquitinating enzymes, deubiquitination, disease progression, substrate specificity, therapeutic targeting, USP10

Impact statement

In this review, we synthesize recent advances in ubiquitin biology through the lens of ubiquitin-specific peptidase 10 (USP10), a context-dependent regulator of normal cell function and disease. Research on USP10 has largely remained divided among cancer, fibrosis, inflammation, metabolism, tissue injury, and cellular stress. We bring these areas together in a unified framework that explains how USP10 may protect cells in some settings yet promote disease in others. We show that USP10's effects are determined by its cellular partners, the type and duration of stress, the stage of disease, and the surrounding tissue environment. By bringing together findings that have often appeared contradictory, this review highlights factors that may influence whether USP10 has protective or disease-promoting effects and identifies settings in which treatment may warrant further investigation. It also connects this framework with emerging strategies aimed at targeting harmful USP10-mediated activity while preserving beneficial functions.

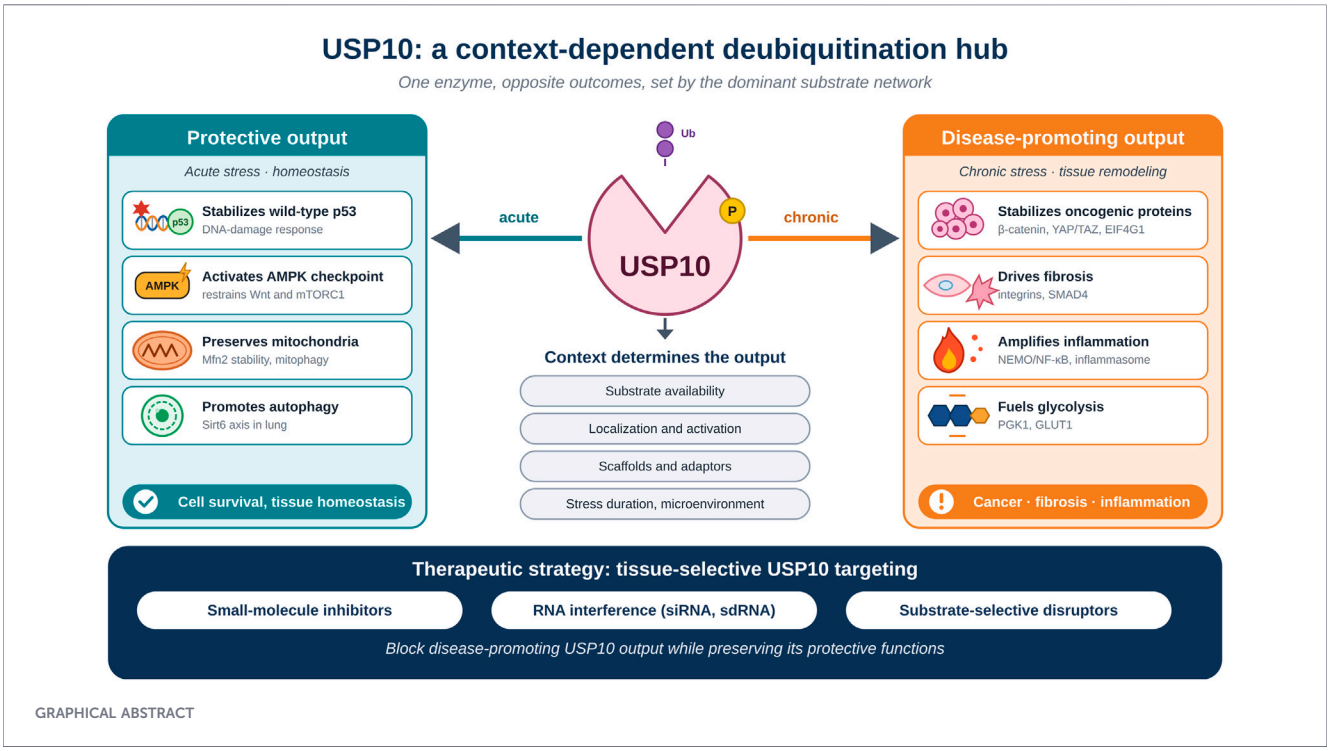
Introduction

Overview

Despite increasing interest in USP10 biology, existing reviews have primarily focused on individual aspects of USP10 function, including cancer progression, stress responses, or therapeutic targeting. A unified framework explaining how USP10 produces distinct, and sometimes opposing, biological outcomes across disease settings remains lacking. This review addresses this gap by examining USP10 as a central regulator linking oncogenic signaling, fibrotic remodeling, mechanotransduction, mitochondrial homeostasis, and cellular stress adaptation. We have synthesized the dual nature of USP10 function by integrating evidence of both protective and pathological roles across diseases and pathologies. USP10 exerts divergent effects depending on cellular environment, disease stage, interacting partners, subcellular localization, and substrate specificity. By consolidating evidence of these opposing outcomes, this review proposes a model emphasizing that USP10 is not inherently protective or pathological, but rather a molecular switch whose functional output is defined by biological context.

Ubiquitination in health and disease

Ubiquitination is a highly regulated process that is mediated by ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin ligase (E3) enzymes that modify proteins to regulate their stability, interactions, localization, and activity [1–3]. Ubiquitin-mediated regulation supports critical cellular functions such as development, stress responses, and immune signaling; ubiquitin-mediated dysregulation contributes to diverse pathologies, including cancer [4–13], neurodegeneration [14–21], fibrosis [22–26], and inflammation [27–31]. Deubiquitinating enzymes (DUBs) remove ubiquitin from substrates, providing dynamic control over protein fate [3]. Their activity is regulated in response to cellular signals through protein-protein interactions, post-translational modifications, and subcellular re-localization. Cysteine proteases, the largest family of DUBs, are particularly sensitive to oxidative stress, as reactive oxygen species can directly modify their catalytic cysteine residues, altering their enzymatic functions [32]. DUBs have been implicated in numerous diseases, including cancers, fibrosis and neurodegenerative disorders; their substrate



GRAPHICAL ABSTRACT

specificities and roles in cellular regulation make them attractive targets for therapeutic development [33]. Among these, USP10 (ubiquitin-specific peptidase 10) plays a context-dependent role in cellular homeostasis, acting as a protective regulator in some settings while promoting fibrotic or oncogenic signaling in others. Understanding USP10 biology is essential to guide USP10-targeted therapeutic intervention.

USP10 structure and its substrates

The human genome encodes 100 active DUBs, counterbalancing the activity of ubiquitin E3 ligases and play essential roles in maintaining protein homeostasis. DUBs are classified into seven families based on sequence and structural features: ubiquitin-specific proteases (USPs), ubiquitin C-terminal hydrolases (UCHs), ovarian tumor proteases (OTUs), Machado–Joseph disease proteases (MJDs, also termed the Josephin family), motif-interacting-with-ubiquitin-containing novel DUB family (MINDY) enzymes, zinc finger with UFM1-specific peptidase domain protein (ZUFSP/ZUP1), and JAB1/MPN/MOV34 metalloenzymes (JAMM/MPN$^+$) [1, 32, 34, 35]. Six of these families are cysteine proteases, whereas JAMM/MPN$^+$ enzymes are zinc-dependent metalloproteases. The families differ in their catalytic mechanisms and in their preferences for ubiquitin-chain linkage. For example, OTU-family enzymes frequently show strong linkage selectivity, MINDY enzymes preferentially cleave long K48-linked chains, and ZUFSP/ZUP1 acts on K63-linked chains and contributes to genome stability. USPs are the largest family and generally show broader linkage tolerance, with substrate selectivity often conferred by regions outside the catalytic domain. DUBs process ubiquitin precursors, recycle ubiquitin, reverse ubiquitin and ubiquitin-like modifications on target proteins, and disassemble unanchored polyubiquitin chains. They function analogously to phosphatases in kinase signaling, fine-tuning protein stability and signaling. USP10 belongs to the USP family [35–38]. DUBs process ubiquitin precursors into mature monomers, recycle ubiquitin, reverse ubiquitin and ubiquitin-like modifications on target proteins, and disassemble unanchored polyubiquitin chains to replenish the monoubiquitin pool. DUBs function analogously to phosphatases in kinase signaling cascades, thereby fine-tuning protein stability and cellular signaling pathways [35, 39, 40].

Cysteine protease DUBs, including USPs such as USP10, remove ubiquitin from target proteins by hydrolyzing the isopeptide bond between ubiquitin and its substrate. This reaction depends on a conserved catalytic cysteine, typically supported by histidine and other catalytic residues that form the active site. Substrate binding promotes conformational changes that position the ubiquitin C-terminal glycine within the catalytic pocket, allowing cleavage of the ubiquitin-substrate linkage. Through this mechanism, DUBs reverse ubiquitination and regulate protein stability, localization, signaling activity, and cellular stress responses. [32, 35]. In addition to the USP catalytic domain, accessory ubiquitin-binding motifs such as ubiquitin-associated (UBA) domains, ubiquitin-interacting motifs (UIMs), and zinc finger ubiquitin-specific protease (ZnF-UBP) domains enhance substrate specificity and facilitate recognition of distinct ubiquitin chain linkages [41]. USP10, a 798-amino-acid ubiquitin-specific protease (Figure 1A), is expressed in the cytoplasm and nucleus of most cell types and is highly conserved across species (~99% identity with rodent homologs) [9, 42]. Structurally, USP10 contains an N-terminal regulatory region and a C-terminal ubiquitin-specific protease (USP) catalytic domain. The USP catalytic domain spans ca. residues 415–795 and forms the core region. Within this domain, the catalytic active site contains a cysteine residue at position 424 that functions as the catalytic nucleophile required for deubiquitinating activity (Figure 1A). Through its cysteine protease activity, USP10 regulates the stability, localization, and activity of numerous protein substrates, influencing processes ranging from stress responses to tumor progression [42, 43]. Structural modeling further supports this domain organization. The predicted three-dimensional structure of human USP10 generated using AlphaFold indicates regions of varying structural confidence, with highly ordered domains predicted with high confidence and several flexible regions showing lower confidence scores (Figure 1B). Consistent with its diverse biological roles, protein–protein interaction analyses [44] reveal that USP10 participates in an extensive interaction network with multiple regulatory partners. Network analysis identifies both direct and secondary interactors associated with USP10, highlighting its integration into broader signaling and regulatory pathways (Figure 1C). Functional enrichment of this interaction network indicates significant associations with pathways related to ubiquitin-mediated protein regulation and cellular stress responses (Figure 1D).

Context-specific functions of USP10

The context-dependent role of USP10 arises from differences in the cellular signaling environment that regulate substrate availability, protein-protein interactions, subcellular localization, and the downstream pathways influenced by USP10-mediated deubiquitination. USP10 does not function as an inherently tumor-suppressive or oncogenic enzyme; rather, its biological outcome is determined by the specific substrates stabilized and the signaling networks that are active within a given cellular context.

Protective functions of USP10 in different cellular contexts

Protective role of USP10 in p53 regulation

The tumor suppressor p53 serves as a barrier to cancer initiation and progression by functioning as a sequence-specific transcription factor [45–47]. Its regulation of expression, activity, and subcellular distribution is largely governed by posttranslational modifications [48–51], including phosphorylation, acetylation [52, 53], and ubiquitination [54–59], which collectively control its stability and transcriptional output. p53 activates genes involved in cell-cycle arrest, apoptosis, DNA repair, and senescence, thereby orchestrating multiple antitumor responses. In addition to its canonical role in tumor suppression, p53 also regulates metabolic and activation states in non-malignant tissues, including fibroblast function during injury responses. In cardiac fibroblasts, p53 acts as a key regulator of cellular metabolism and activation, where its activity

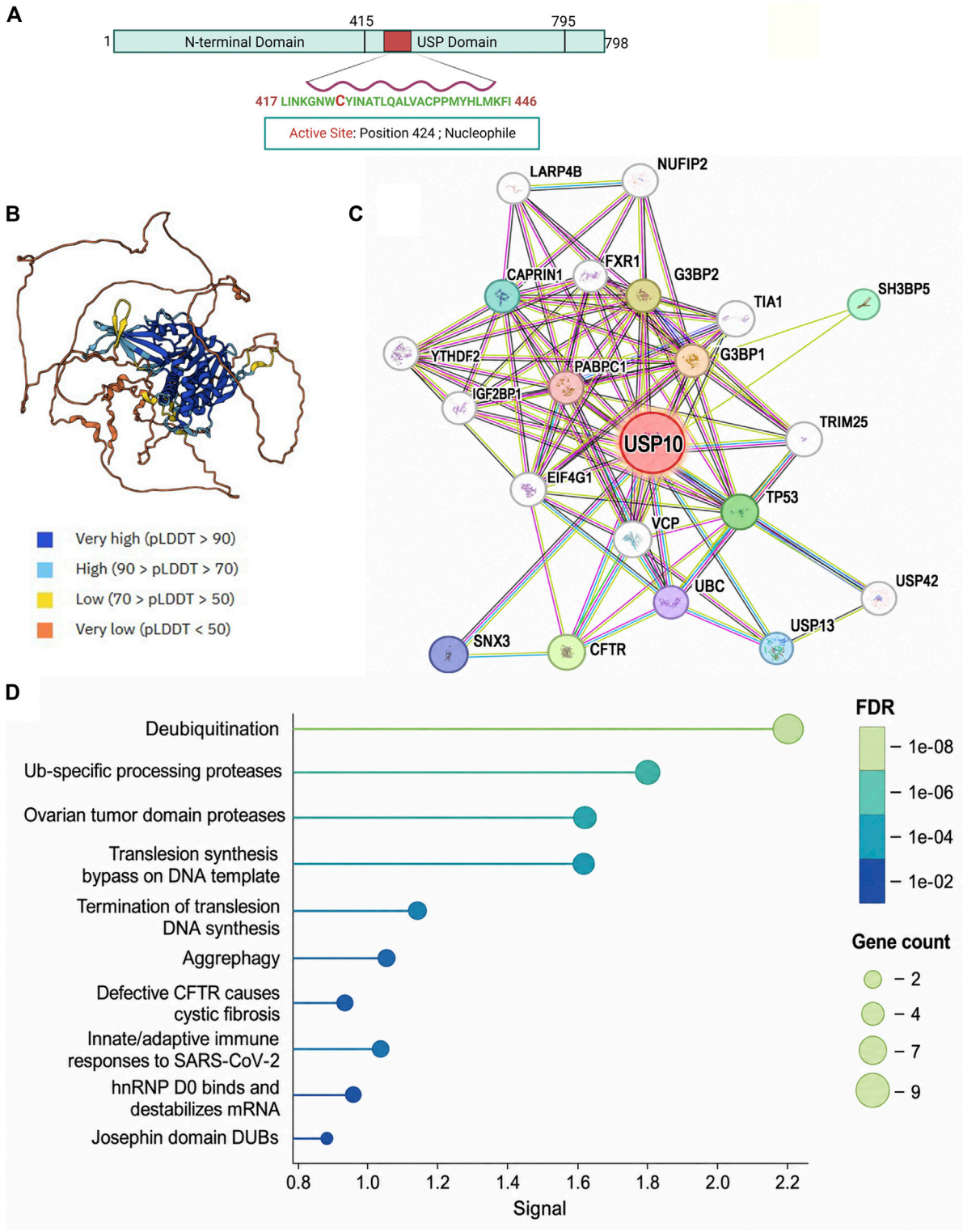


FIGURE 1
Structural features, interaction network, and functional enrichment of USP10. **(A)** The human USP10 protein has an N-terminal regulatory region and a C-terminal ubiquitin-specific protease (USP) catalytic domain. The catalytic USP domain spans residues 415–795 and contains the active-site cysteine at position 424 (denoted in red), which is required for its DUB activity. **(B)** Predicted three-dimensional structure of the human USP10 isoform USP10-201, generated using AlphaFold v2.3.2 and obtained from. The Human Protein Atlas. Levels for confidence in the model are presented in colors representing very high (blue) to very low (brown) confidence. **(C)** A protein–protein interaction (PPI) network centered on USP10 was generated using the STRING database. In this network, nodes represent proteins and edges represent predicted or experimentally supported interactions. The colored edges indicate different sources of interaction evidence, such as experimental data, curated databases, or computational predictions. The colored nodes correspond to the query protein (USP10) and its first shell interactors, which are proteins that directly interact with USP10. The second shell interactors, shown as white nodes, represent proteins that interact with the first shell proteins but do not necessarily interact directly with USP10. **(D)** Reactome
(*Continued*)

FIGURE 1 (Continued)
pathway enrichment analysis of differentially regulated genes. Bubble plot showing significantly enriched Reactome pathways ranked by enrichment signal (x-axis). Each dot represents a pathway term, with the x-axis indicating enrichment strength ("Signal"). Bubble size corresponds to the number of genes contributing to each pathway (gene count), while color intensity reflects statistical significance after multiple testing correction (FDR; darker shades indicate lower FDR and higher significance, as shown in the color scale). Pathways are grouped based on similarity (cutoff ≥0.8), indicated by horizontal grouping bands on the right. Top enriched pathways include deubiquitination and ubiquitin-specific processing proteases. USP10, Ubiquitin-specific peptidase 10; pLDDT, predicted Local Distance Difference Test; FDR, False Discovery Rate.

contributes to the control of fibroblast-to-myofibroblast transition and tissue remodeling. Within this regulatory network, USP10 is a deubiquitinating enzyme that protects p53 homeostasis in unstressed cells and represents one of the first documented DUBs acting on cytoplasmic p53 [60]. Following DNA damage, USP10 is phosphorylated by ataxia telangiectasia mutated (ATM) kinase at Thr42 and Ser337, promoting USP10 stabilization and nuclear translocation. Once in the nucleus, USP10 enhances p53 activation by deubiquitinating and stabilizing p53, complementing other ATM-dependent mechanisms, including direct p53 phosphorylation and destabilization of mouse double minute 2 homolog (MDM2), a major negative regulator of p53 [61] (Figures 2A,B). This USP10-p53 axis also extends beyond cancer. In cardiac fibroblasts, Mao et al. identified a scaffold-dependent mechanism in which Heat Shock Protein Family A (Hsp70) Member 12A (HSPA12A), a stress-responsive heat shock protein enriched in the heart, facilitates the interaction between USP10 and p53 during cardiac stress [60]. Rather than acting only as a chaperone, HSPA12A functions as a signaling scaffold that promotes USP10-mediated stabilization of p53. Stabilized p53 suppresses glycolytic metabolism, limits fibroblast activation, and reduces myofibroblast marker expression, thereby restraining post–myocardial infarction remodeling (Figure 2B). Notably, HSPA12A expression decreases during fibroblast activation, and loss of this scaffold exacerbates fibrotic remodeling, suggesting that preservation of USP10-p53 signaling can exert protective effects in non-malignant tissue injury responses. Consistent with a protective role for USP10 in p53-dependent tumor suppression, USP10 downregulation has been observed in renal cell carcinoma (RCC) [62], suggesting that loss of USP10 may attenuate p53 activity and promote tumorigenesis in p53-wild-type contexts. Collectively, these findings position USP10 as a stress-responsive regulator of p53 signaling and a context-dependent tumor suppressor. Although USP10 can exert protective effects through non–p53-dependent pathways, its tumor-suppressive activity appears most closely linked to preservation of p53-dependent stress-response signaling.

Protective role of USP10 in AMPK signaling in cancer

AMP-activated protein kinase (AMPK) is a highly conserved serine/threonine kinase that functions as a central sensor of cellular energy status and regulates multiple biological processes beyond metabolism [63–65]. AMPK is activated under conditions of energy stress characterized by increased AMP/ADP levels, which promote phosphorylation by upstream kinases, primarily liver kinase B1 (LKB1) [66, 67]. Once activated, AMPK restores energy homeostasis by stimulating ATP-generating catabolic pathways while suppressing energy-consuming anabolic processes. Beyond its metabolic role, AMPK also regulates autophagy, immune responses, and extracellular matrix homeostasis [68–74], and has been implicated as a key inhibitor of myofibroblast differentiation and fibrotic progression across multiple organs [68, 75–79]. Given these pleiotropic functions in stress adaptation and tissue remodeling, AMPK represents an important signaling node in fibrosis-associated pathways and provides a relevant framework for understanding its interaction with USP10-mediated regulatory mechanisms.

USP10 is a positive regulator of AMPK signaling. Deng et al. demonstrated that USP10 promotes AMPK activation (Figure 2C) independent of p53 status [80]. Loss of USP10 significantly reduced phosphorylation of AMPKα and its downstream targets, acetyl-CoA carboxylase 1 (ACC1) and regulatory-associated protein of mTOR (Raptor), leading to lipid droplet accumulation, increased lactate production, and upregulation of glycolytic gene expression. Mechanistically, the AMPK α subunit is predominantly modified by polyubiquitination at K63, a non-proteolytic modification that limits access of LKB1 to Thr172 of AMPK under basal conditions [81]. During energy stress, USP10 is upregulated and removes these ubiquitin chains, enabling LKB1-mediated phosphorylation and activation of AMPK without altering total AMPK protein levels. This regulation is independent of K48-linked ubiquitination and proteasomal degradation, indicating a direct control of signaling [81, 82].

Simultaneously, AMPK also regulates USP10 through a feedforward activation loop in which AMPK phosphorylates USP10 at Ser76 at an N-terminal region that matches the AMPK consensus motif. Mutation of Ser76 to alanine abolished USP10 phosphorylation and impaired its deubiquitinase activity. These data identify Ser76 phosphorylation as a key regulatory event that enhances USP10 activity. Because USP10 also stabilizes p53 as described before, the AMPK/USP10 axis links metabolic stress sensing with tumor-suppressive signaling pathways [80].

The USP10-AMPK axis has a tumor-suppressive, protective function that limits colorectal cancer (CRC) progression by coupling metabolic control to inhibition of oncogenic signaling programs, including the Wnt/β-catenin pathway. Tumor progression in CRC requires coordinated activation of anabolic metabolism together with Wnt/β-catenin-driven transcriptional programs that promote proliferation and survival. Wang et al. demonstrated that USP10 serves as a molecular bridge linking these two pathways, with sequential phosphorylation events enhancing its DUB activity. Phosphorylated/activated USP10 enables AMPK to suppress Wnt/β-catenin signaling through stabilization of axis inhibition protein 1 (Axin1), a key negative regulator of the pathway [83]. Consistently, LKB1, phosphorylated AMPK, USP10, and Axin1 expression are positively correlated in human CRC specimens, supporting the

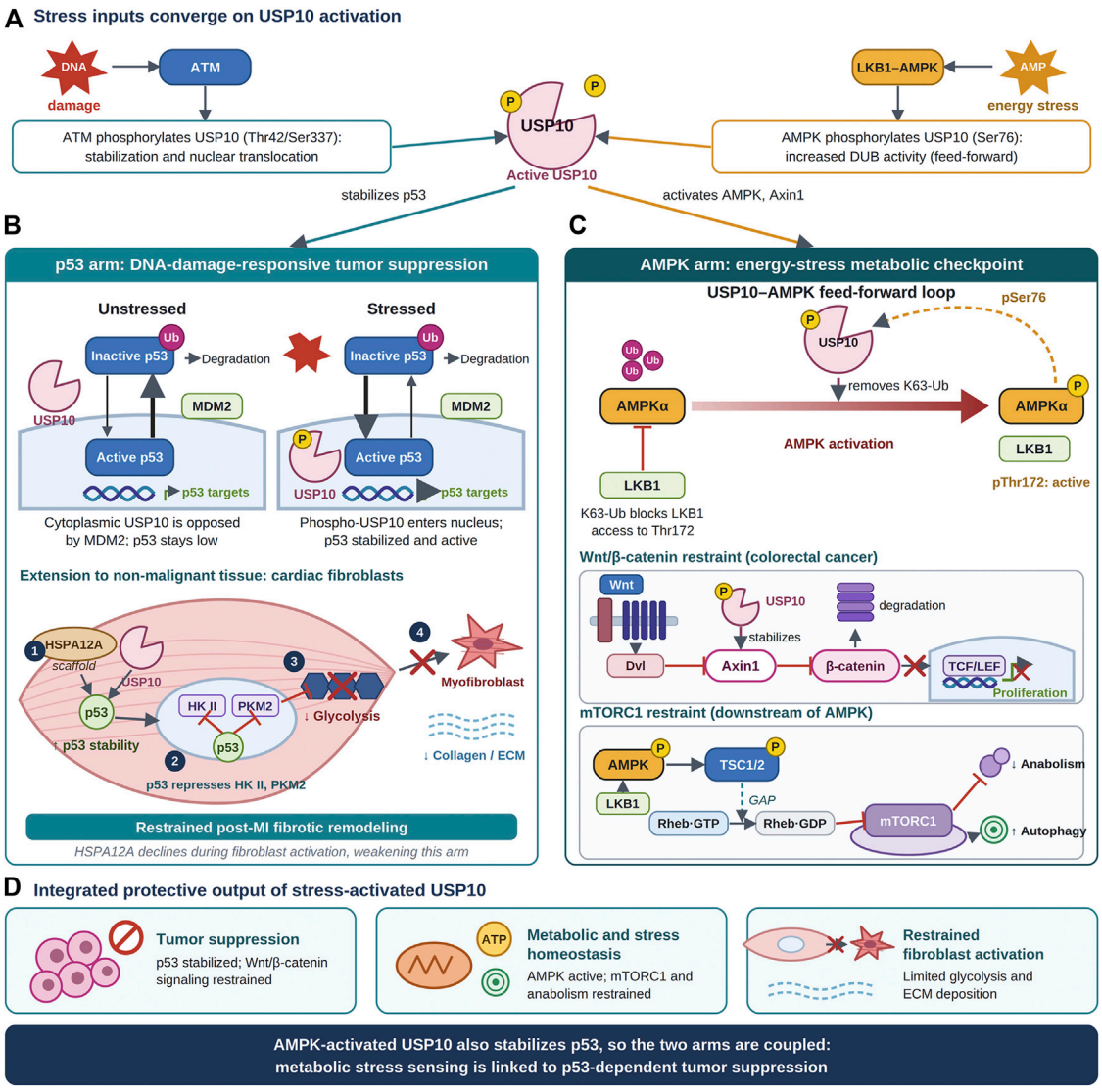


FIGURE 2
Integrated protective axes of USP10: stress-activated p53 and AMPK signaling. **(A)** Two stress inputs converge on USP10 activation. DNA damage activates ATM, which phosphorylates USP10 at Thr42 and Ser337, promoting USP10 stabilization and nuclear translocation. Energy stress (increased AMP) activates LKB1–AMPK, which phosphorylates USP10 at Ser76 and increases its deubiquitinase (DUB) activity, forming a feed-forward loop. Active USP10 stabilizes p53 (panel B) and activates AMPK and Axin1 (panel C). **(B)** The p53 arm: DNA-damage-responsive tumor suppression. In unstressed cells, USP10 is mainly cytoplasmic and its activity toward p53 is opposed by MDM2, which ubiquitinates p53 and drives its nuclear export and degradation, so p53 levels and target gene transcription remain low. Under stress, phosphorylated USP10 enters the nucleus, shifting the balance from MDM2-mediated ubiquitination toward USP10-mediated deubiquitination. p53 is then stabilized and drives transcription of its target genes. The arm extends to non-malignant tissue in cardiac fibroblasts. (1) The stress-responsive scaffold HSPA12A promotes the interaction between USP10 and p53 and increases p53 stability. (2) Stabilized p53 represses the glycolytic enzymes HK II and PKM2. (3) Glycolysis is reduced. (4) Glycolysis-dependent myofibroblast activation and collagen/ECM deposition are limited, restraining post-MI fibrotic remodeling. HSPA12A declines during fibroblast activation, which weakens this arm. **(C)** The AMPK arm: energy-stress metabolic checkpoint. Under basal conditions, K63-linked ubiquitination of AMPKα blocks LKB1 access to Thr172. USP10 removes these K63-linked chains, allowing LKB1 to phosphorylate Thr172 and activate AMPK. Active AMPK in turn phosphorylates USP10 at Ser76 (dashed arrow), closing the USP10–AMPK feed-forward loop. Wnt/β-catenin restraint (colorectal cancer): phosphorylated USP10 stabilizes Axin1, a negative regulator of Wnt signaling that is inhibited by Dishevelled (Dvl) downstream of the Wnt receptor. Stabilized Axin1 promotes β-catenin degradation, blocking TCF/LEF-driven transcription and proliferation. mTORC1 restraint (downstream of AMPK): AMPK phosphorylates TSC2, activating the TSC1/2 complex, which acts as a GAP to convert Rheb-GTP to Rheb-GDP and thereby inhibits mTORC1. This reduces anabolism and increases autophagy. **(D)** Integrated protective output of stress-activated USP10: tumor suppression (stabilized p53 and restrained Wnt/β-catenin signaling), metabolic and stress homeostasis (active AMPK with restrained mTORC1 and anabolism), and restrained fibroblast activation (limited glycolysis and ECM deposition). Because AMPK-activated USP10 also stabilizes p53, the two arms are coupled, linking metabolic stress sensing to p53-dependent tumor suppression. AMPK, AMP-activated protein kinase; AMP, adenosine monophosphate; ATM, ataxia telangiectasia mutated; ATP, adenosine triphosphate; DUB, deubiquitinase; Dvl, Dishevelled; ECM, extracellular matrix; GAP, GTPase-activating protein; GDP, guanosine diphosphate; GTP, guanosine triphosphate; HK II, hexokinase 2; HSPA12A, heat shock protein family A (Hsp70) member 12A; LKB1, liver kinase B1; MDM2, mouse double minute 2 homolog; MI, myocardial infarction; mTORC1, mechanistic target of rapamycin complex 1; P, phosphorylation; PKM2, pyruvate kinase M2; Rheb, Ras homolog enriched in brain; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; TSC, tuberous sclerosis complex; Ub, ubiquitin.

existence of an integrated LKB1-AMPK-USP10 signaling axis that restrains tumor growth [83].

In addition to regulating Wnt/β-catenin signaling, AMPK also limits tumor-promoting anabolic metabolism through the canonical TSC1/2-mTORC1 pathway. Activated AMPK phosphorylates tuberin protein (TSC2), promoting the formation and activity of the Tuberous Sclerosis Complex (TSC1/2). This complex functions as a GTPase-activating protein (GAP) for Ras homolog (Rheb), converting Rheb from its active GTP-bound form to the inactive GDP-bound state, thereby suppressing mTORC1 signaling. Inhibition of mTORC1 consequently reduces anabolic metabolism, leading to decreased protein synthesis, slower cell growth, reduced lipid and nucleotide synthesis, and increased autophagy (Figure 2C) [83]. Collectively, the USP10-AMPK axis positions AMPK as the central signaling hub that integrates energy stress sensing with coordinated suppression of Wnt/β-catenin–driven transcriptional programs and mTORC1-mediated anabolic metabolism, thereby reprogramming tumor cell behavior toward a growth-restricted, energy-conserving state in colorectal cancer. Stress-activated USP10 integrates tumor suppression, metabolic homeostasis, and restraint of fibroblast activation. By stabilizing p53 and regulating Wnt/β-catenin signaling, USP10 supports tumor suppression, while AMPK activation helps maintain metabolic balance and restrain mTORC1 signaling. In parallel in a cardiac cell model, USP10 may limit fibroblast activation by reducing glycolytic activity and extracellular matrix deposition. AMPK-mediated USP10 activation may further reinforce p53 stability, linking metabolic stress sensing to p53-dependent tumor suppression (Figure 2D).

Protective role of USP10 in non-malignant conditions

Extending beyond p53-and AMPK-dependent regulation of oncogenic and metabolic pathways in cancer, USP10 also maintains cellular homeostasis across diverse non-malignant tissues, like in the central nervous system. In these contexts, its activity is not limited to tumor suppression but instead preserves cellular viability under environmental and oxidative stress.

In neurologic settings, USP10 plays a critical role in maintaining redox balance and enhancing neuronal survival under conditions of oxidative injury. Sango et al. demonstrated that USP10 supports antioxidant defense mechanisms during dopamine-induced oxidative stress through activation of nuclear factor erythroid 2-related factor 2 (NRF2) signaling [84]. Mechanistically, USP10 interacts with the NRF2 adaptor protein p62, promotes p62 phosphorylation, and stabilizes p62–Keap1 interactions, thereby facilitating NRF2 activation and enhancing transcription of antioxidant response genes. In parallel, USP10 also enhances NRF2 translational efficiency, collectively amplifying antioxidant capacity. This coordinated activation of NRF2-dependent transcription reduces intracellular reactive oxygen species (ROS) accumulation and limits ROS-induced neuronal apoptosis [84]. The protective roles of USP10 in multiple disease contexts are summarized in Table 1.

Protective role of USP10 in fibrosis

Fibrosis is a maladaptive response to chronic injury characterized by persistent fibroblast activation, differentiation into contractile extracellular matrix (ECM)-secreting myofibroblasts, excessive deposition of ECM components including collagen I and III, and progressive disruption of tissue architecture across multiple organs, including the liver, lung, kidney, heart, and cornea. Fibrotic progression is driven by a complex interplay of unresolved inflammation, profibrotic cytokine signaling, cellular stress responses, and mechanical cues [98–101]. Although most studies linking USP10 to fibrosis and inflammation suggest a pathological role (see below), one study indicates a protective function. USP10 expression is reduced in lungs from patients with idiopathic pulmonary fibrosis (IPF) and in bleomycin-induced pulmonary fibrosis models. Restoration of USP10 attenuates collagen accumulation and suppresses fibrotic progression by enhancing autophagic activity. Mechanistically, USP10 stabilizes Sirtuin 6 (Sirt6), leading to inhibition of Sirt6-dependent AKT/mTOR signaling and restoration of autophagic flux. Importantly, inhibition of autophagy abolishes the protective effects of USP10, demonstrating that USP10-mediated regulation of autophagy plays a role in its antifibrotic function [87].

Protective role of USP10 in mitochondrial regulation

Mitochondrial fission, fusion, and mitophagy are essential for maintaining cellular energy homeostasis and stress adaptation [102–104], and disruption of these processes contributes to ischemic injury [105], cardiac remodeling [106], neurodegeneration [107], metabolic disease [108, 109], and fibrosis [110–113]. USP10 has emerged as an important regulator of mitochondrial homeostasis under stress conditions (Figure 3A). Under physiological conditions, USP10 directly interacts with and stabilizes mitofusin 2 (Mfn2), a key mediator of mitochondrial fusion, by removing K11- and K48-linked ubiquitin chains and preventing its proteasomal degradation. Loss of Mfn2 abolishes USP10-mediated protection, identifying Mfn2 as a critical downstream effector of USP10-dependent mitochondrial regulation. This protective mechanism is impaired during cardiac pressure overload, where USP10 expression is reduced, in part through impaired Yin Yang 1 (YY1)-dependent transcriptional regulation. Reduced USP10 promotes cytoplasmic degradation of Mfn2, leading to abnormal mitochondrial structure and function and contributing to cardiac dysfunction [114, 115] (Figure 3B). USP10 also supports mitochondrial quality control in ischemic injury. In ischemic stroke models, tetrahydroxystilbene glucoside (TSG) promotes neuroprotection through a USP10-dependent pathway. Mechanistically, USP10 stabilizes Y-box binding protein 1 (YBX1), preventing its ubiquitin-mediated degradation and enabling activation of PTEN-induced kinase 1 (PINK1)/Parkin-mediated mitophagy. Disruption of this axis blocks USP10-driven mitophagy and abolishes neuroprotection, demonstrating that USP10-dependent stabilization of YBX1 is required for mitochondrial quality control following ischemic stress [116].

TABLE 1 Summary of key findings - USP10 protective roles.

Disease/ context	Key findings upon USP10 OE	Mechanism/ pathway	Perturbation method reported	Level(s) of reported change	Model system	References
Thyroid cancer	Increasing USP10 expression or inhibiting ABCG2 could be used as novel targets for treating DOX-resistant thyroid cancer	Overexpressing USP10 inhibited PI3K/ AKT pathway by activating PTEN	USP10 overexpression; ABCG2 inhibition (specific reagent not stated in table)	Protein: PTEN/USP10-related effects implied; Pathway: PI3K/AKT inhibition. mRNA and enzyme activity: not specified	Human thyroid cancer cell lines	[85]
Diabetic vascular calcification (VC)	USP10 overexpression alleviates vascular calcification and inhibits osteogenic differentiation of VSMCs	USP10 directly interacts with and deubiquitinates AMPKα, enhancing AMPKα phosphorylation at Thr172 which leads to activation of AMPK signaling and inhibition of calcification. Pharmacologic AMPK inhibition reverses USP10's protective effect	USP10 overexpression; pharmacological AMPK inhibition	Protein: AMPKα deubiquitination/ phosphorylation; Enzymatic activity: AMPK signaling activation; Pathway: reduced calcification	Diabetic athero-sclerosis mouse models	[86]
Idiopathic Pulmonary Fibrosis (IPF)	USP10 overexpression alleviates lung injury and collagen deposition and enhances autophagy in fibrotic lungs	USP10 interacts with and stabilizes Sirt6 by preventing its ubiquitin-mediated degradation; activation of Sirt6 inhibits the AKT/mTOR pathway, thereby promoting autophagy; reduced fibroblast activation and fibrosis. The protective effect is lost when autophagy is inhibited (3-MA)	USP10 restoration/ overexpression; 3-MA autophagy inhibition	Protein: SIRT6 stabilization; Pathway: AKT/mTOR and autophagy; Functional: reduced fibroblast activation/ fibrosis	Normal or IPF human lung samples, wild-type mice	[87]
Nonalcoholic fatty liver disease (NAFLD)	USP10 overexpression alleviates hepatic steatosis, insulin resistance, and inflammation, while deficiency worsens these metabolic dysfunctions	USP10 interacts with and deubiquitinates Sirt6, preventing its degradation leading to stabilized Sirt6, suppresses lipid accumulation and inflammatory signaling. The protective effect of USP10 is abolished when Sirt6 is knocked down	USP10 overexpression/ deficiency; SIRT6 knockdown	Protein: SIRT6 stability; Pathway: lipid/ inflammatory signaling; Functional: steatosis and metabolic outcomes	Liver samples from NAFLD patients, mouse model	[88]

(*Continued*)

TABLE 1 Continued

Disease/ context	Key findings upon USP10 OE	Mechanism/ pathway	Perturbation method reported	Level(s) of reported change	Model system	References
Nonalcoholic steatohepatitis (NASH)/ Nonalcoholic fatty liver disease (NAFLD)	USP10 overexpression enhances autophagy, leading to reduced hepatic steatosis, inflammation, and fibrosis	USP10 upregulates autophagy-related pathways, promotes autophagosome synthesis, and restores autophagic flux during NASH progression. The lipid-lowering effect of USP10 is autophagy dependent, as it is abolished by autophagy inhibitors (independent of β-oxidation changes)	USP10 overexpression; autophagy inhibitors	Pathway: autophagy/ autophagic flux; Functional: hepatic steatosis, inflammation and fibrosis. Other levels not specified	Wild-type mice, HepG2 cells	[89]
Type 2 diabetes mellitus (T2DM)–associated myocardial infarction (MI)	USP10 upregulation protects against MI-induced cardiac dysfunction in T2DM by reducing myocardial apoptosis and fibrosis	FSTL1 activates the USP10/Notch1 signaling axis. USP10 deubiquitinates and stabilizes NICD1 (Notch1 intracellular domain) leading to enhanced Notch signaling attenuates fibrosis and apoptosis in cardiac fibroblasts. Pharmacologic inhibition of Notch1 (crenigacestat) or USP10 (spautin-1) abolishes FSTL1's cardioprotective effects	FSTL1 stimulation; USP10/Notch inhibition with Spautin-1/ crenigacestat	Protein: NICD1 stabilization; Pathway: Notch signaling; Functional: apoptosis, fibrosis and cardiac function	Diabetic mouse models	[90]
Cardiac hypertrophy	USP10 activation (via limonin) prevents cardiac hypertrophy, improves cardiac function, and reduces hypertrophic markers	Limonin activates USP10, which deubiquitinates and stabilizes Sirt6, preventing its proteasomal degradation. Stabilized Sirt6 enhances PPARα activity, suppressing hypertrophic signaling. USP10 knockdown (siRNA) abolishes limonin's anti-hypertrophic effects	Limonin treatment; USP10 siRNA.	Protein: SIRT6 stability; Enzymatic activity: USP10 activation is described, but direct assay details not specified; Pathway: PPARα/hypertrophy	Neonatal rat cardiac myocytes (NRCMs, wild-type mice	[91]

(*Continued*)

TABLE 1 Continued

Disease/ context	Key findings upon USP10 OE	Mechanism/ pathway	Perturbation method reported	Level(s) of reported change	Model system	References
Ischemic stroke	USP10 upregulation mediates the neuroprotective effects of VNS, reducing infarct volume and improving neurological recovery	VNS increases USP10 expression, which inhibits NF-κB signaling, thereby suppressing pro-inflammatory cytokine release and glial activation (microglia and astrocytes). Silencing USP10 abolishes the anti-inflammatory and neuroprotective effects of VNS.	Vagus nerve stimulation; USP10 silencing (method not specified in table)	Protein/expression: USP10 expression; Pathway: NF-κB; Functional: infarct volume, glial activation, neurological recovery	Transient middle cerebral artery occlusion mouse model	[92]
Nonalcoholic fatty liver disease (NAFLD)	USP10 overexpression alleviates hepatocellular steatosis by restoring autophagic activity and lipid-targeted autophagy	USP10 promotes autophagosome synthesis and degradation, enhancing autophagic flux. The effect is autophagy-dependent, mediated via JNK1/TSC2 signaling pathways; inhibition of JNK1 impairs autophagy, but TSC2 compensates in early stages. Autophagy inhibitors abolish USP10's lipid-lowering effects	USP10 overexpression; JNK1 inhibition; autophagy inhibitors	Pathway: JNK1/ TSC2 and autophagy; Functional: lipid accumulation/steatosis. Molecular level not otherwise specified	HepG2 cells treated with palmitic acid (PA)	[93]
Hepatic ischemia/ reperfusion (I/R) injury	USP10 overexpression protects against hepatic I/ R injury, reducing hepatocyte apoptosis and liver inflammation	USP10 inhibits activation of the TAK1–JNK/ p38 signaling pathway, thereby suppressing NF-κB-mediated inflammation and apoptosis. Knockdown of USP10 exacerbates injury, while TAK1 inhibition abolishes USP10's protective effects	USP10 overexpression/ knockdown; TAK1 inhibition	Pathway: TAK1–JNK/ p38 and NF-κB; Functional: apoptosis and tissue injury	Mouse hepatic I/R injury model, primary hepatocytes	[94]
Sepsis-induced acute kidney injury (AKI)	USP10 overexpression alleviates renal dysfunction, reduces tubular epithelial cell apoptosis, and mitigates oxidative stress	USP10 stabilizes Sirt6, which activates the NRF2/ HO-1 antioxidant pathway, decreased ROS production, improved cell viability, and reduced apoptosis. USP10 deficiency exacerbates renal injury and oxidative damage	USP10 overexpression/ deficiency	Protein: SIRT6 stabilization; Pathway: NRF2/HO-1; Functional: ROS, viability, apoptosis and renal injury	HK-2 cells, CLP-induced sepsis mouse model	[95]

(*Continued*)

TABLE 1 Continued

Disease/ context	Key findings upon USP10 OE	Mechanism/ pathway	Perturbation method reported	Level(s) of reported change	Model system	References
Parkinson's disease (PD)/ neuronal oxidative stress	USP10 overexpression reduces ROS production and ROS-dependent apoptosis in dopaminergic neurons	USP10 interacts with p62, promoting its phosphorylation; enhanced p62-Keap1 interaction; activation of Nrf2 antioxidant transcriptional activity. USP10 also increases Nrf2 translation, collectively enhancing cellular antioxidant defense	USP10 overexpression; exact perturbation used for individual mechanistic tests not fully specified in table	Protein: p62 phosphorylation/ interaction; mRNA/ translation: increased NRF2 translation (not necessarily NRF2 mRNA); Pathway: NRF2 antioxidant response; Functional: ROS/apoptosis	SH-SY5Y neuro-blastoma cell line	[84]
Cerebral ischemia-reperfusion (I/R) injury	USP10 overexpression protects against cerebral I/R injury, reducing infarct size, neuronal apoptosis, and neurological deficits	USP10 interacts with TAK1, inhibiting activation of the TAK1-JNK/MAPK and NF-κB signaling pathways, thereby suppressing inflammation and apoptosis. USP10 deletion exacerbates injury and inflammatory responses	USP10 overexpression/ deletion	Protein: USP10–TAK1 interaction; Pathway: JNK/MAPK and NF-κB; Functional: infarct size, apoptosis and deficits	Cerebral I/R injury mouse model	[96]
Protein aggregation/ Parkinson's disease (PD)	USP10 overexpression inhibits ubiquitinated protein-induced apoptosis and reduces α-synuclein neurotoxicity	USP10 interacts with p62, enhancing p62-dependent ubiquitinated protein aggregation and aggresome formation (including α-synuclein). Aggresomes suppress proteasome activity, sequester cytotoxic proteins, and promote Lewy body formation, thereby protecting against protein aggregation-linked cytotoxicity	USP10 overexpression	Protein: p62 interaction; Subcellular localization/ organization: aggresome formation and protein sequestration; Functional: apoptosis/ neurotoxicity	HeLa cells	[97]

Pathological functions of USP10 in different cellular contexts

Pathological role of USP10 in cancer progression (p53-dependent)

In contrast to USP10 being a DUB for wild-type p53 and a cancer-suppressor, its stabilization can contribute to cancer progression, via interactions with circular RNAs (circRNAs). Non-coding RNAs, circRNAs, can modulate the stability and function of key components within p53 signaling [117]. circRNAs are covalently closed, single-stranded RNA molecules generated by back-splicing, which lack a 5′ cap and 3′ poly(A) tail [117], whose expression correlates with poor prognosis in head and neck squamous cell carcinoma (HNSCC) [118, 119]. Wang et al. reported the existence of a circRNA derived from the TP53 gene, circTP53. CircTP53 directly interacts with USP10, stabilizing both proteins and enhancing USP10-mediated deubiquitination of p53, thereby preventing its proteasomal degradation and increasing p53 levels. These findings establish the circTP53/USP10/p53 axis as a potential therapeutic target in HNSCC (Figure 4A) [119].

USP10 is also involved in prostate cancer, the most frequently diagnosed malignancy in men, and androgen receptor (AR) signaling is central to its progression. Takayama et al. provided the first evidence linking high USP10 expression with poor

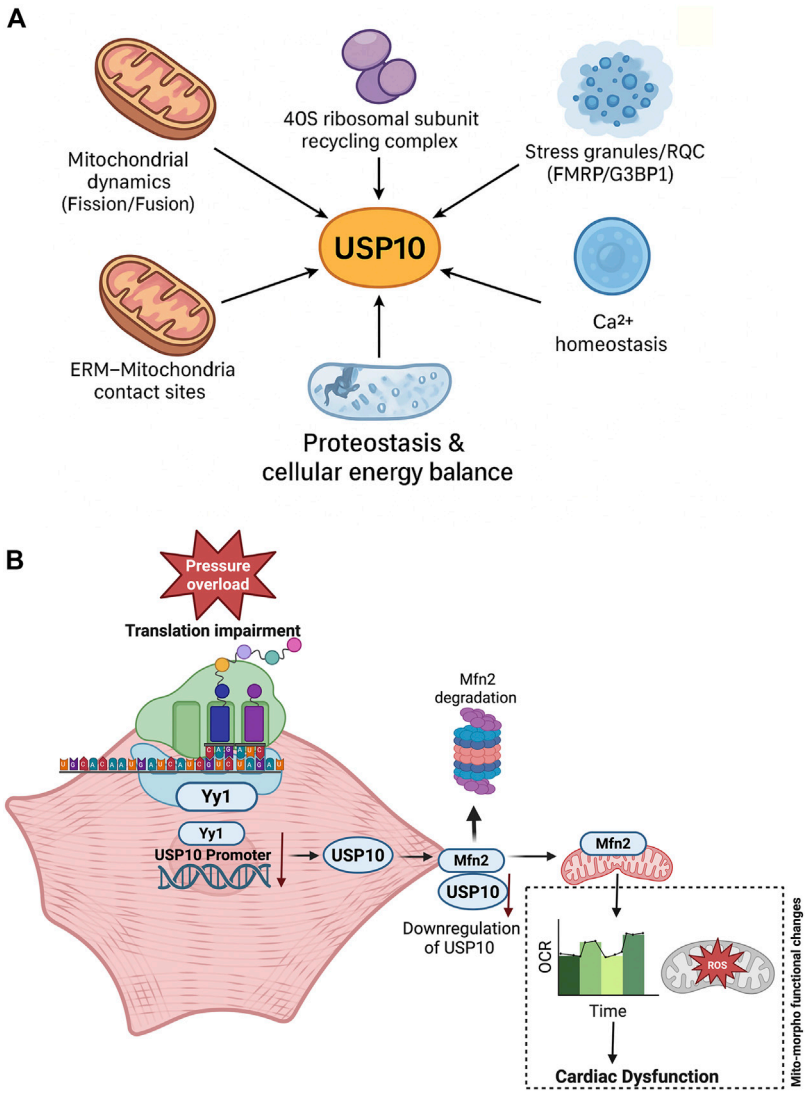


FIGURE 3
USP10 as a Central Mediator of Mitochondrial Homeostasis and Cellular Stress Adaptation. **(A)** Schematic representation illustrating the multifaceted roles of USP10 in maintaining mitochondrial and cellular homeostasis under pathological stress. **(B)** Under physiological conditions, the transcription factor YY1 promotes USP10 transcription, leading to adequate USP10 protein expression. USP10 deubiquitinates Mfn2, removing K11/K48-linked ubiquitin chains and thereby stabilizing Mfn2. This maintains normal mitochondrial fusion dynamics, preserves mitochondrial integrity, and supports healthy cardiac function. In contrast, during cardiac pressure overload, YY1-mediated transcription of USP10 is reduced, resulting in decreased USP10 protein levels. This leads to increased K11/K48-linked ubiquitination of Mfn2, enhanced proteasomal degradation of Mfn2, and consequent disruption of mitochondrial fusion. The resulting mitochondrial structural and functional abnormalities contribute to impaired mitochondrial dynamics, ultimately driving cardiac dysfunction and adverse cardiac remodeling. YY1, Yin Yang 1; Mfn2, Mitofusin-2; K11/K48, Lysine-11/Lysine-48–linked Ubiquitin Chains.

prognosis in prostate cancer [120], suggesting oncogenic roles beyond its established function as a p53 DUB. Mechanistically, USP10 upregulates the AR target, Ras GTPase-activating protein-binding protein 2 (G3BP2) [121], which promotes p53 cytoplasmic export and thereby suppresses p53 activity. USP10 knockdown reduces G3BP2 levels and impairs tumor cell growth, an effect reversed by p53 depletion, underscoring the importance of the USP10/G3BP2/p53 axis [121]. These results indicate that USP10 may promote prostate cancer progression through regulation of G3BP2 and other unidentified oncogenic substrates.

Pathological role of USP10 in cancer progression (p53-independent)

USP10 is primarily deleterious and promotes tumor growth in most cancers, whereas knockdown of USP10 is beneficial, as summarized in Table 2. For instance, in colorectal, lung, liver, pancreatic, breast, prostate, and glioblastoma, USP10, independent of p53, predominantly promotes malignant progression by stabilizing β-catenin, YAP/TAZ, EIF4G1, Smad4, and other oncogenic effectors.

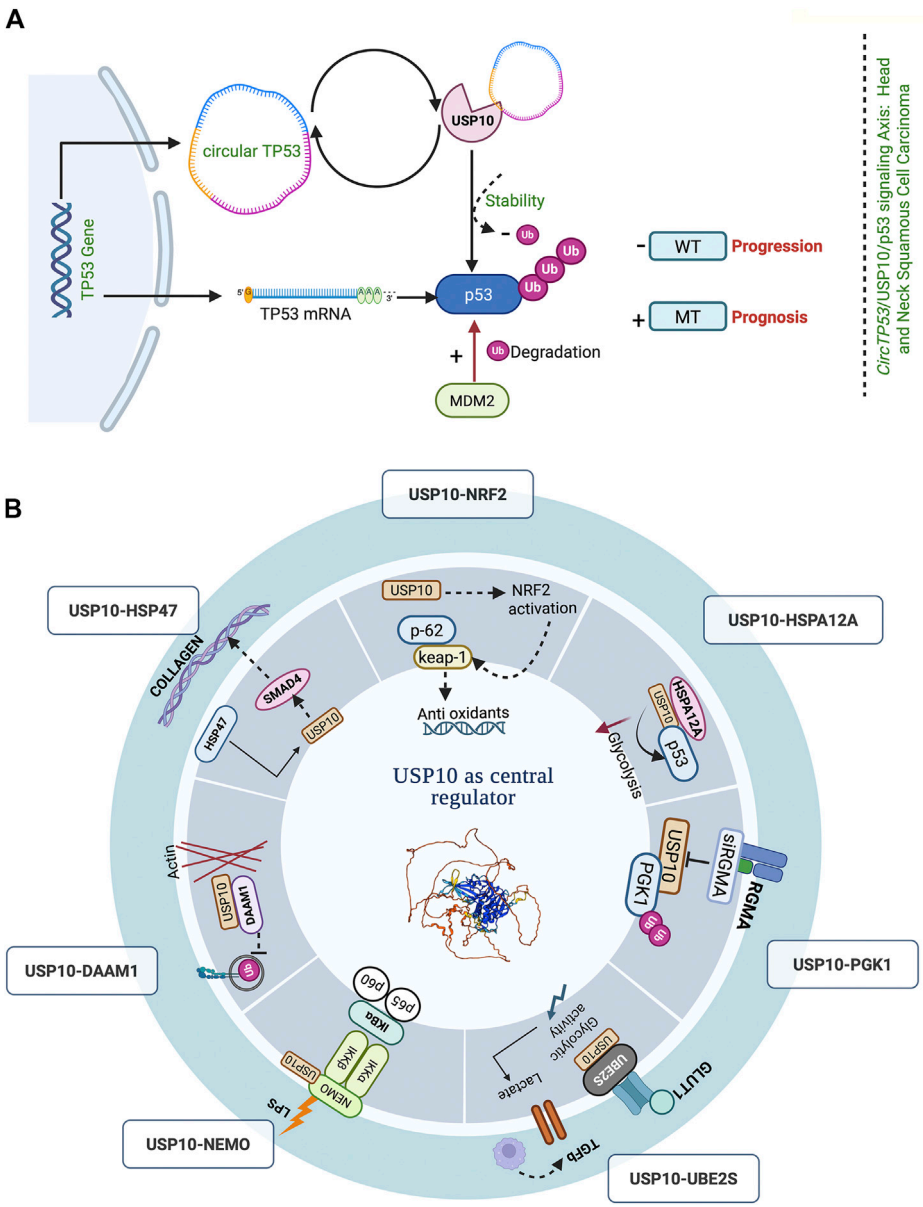


FIGURE 4
Diverse roles of USP10 in circTP53-mediated carcinoma, metabolic reprogramming, inflammation, fibrosis, and stress responses. **(A)** A circular RNA derived from the TP53 gene (circTP53) is upregulated in HNSCC and is associated with poor patient prognosis. circTP53 interacts with USP10, leading to their mutual stabilization and enhanced deubiquitinase activity of USP10 toward p53. In tumor cells harboring wild type p53, circTP53 suppresses cell viability and inhibits tumor growth, whereas in cells with mutant p53, it exerts the opposite effect, promoting cell viability and tumor progression. **(B)** USP10 integrates diverse stress-response and disease-related signaling pathways. In neurons, it reduces dopamine-induced oxidative stress and apoptosis by enhancing p62-Keap1-Nrf2 antioxidant signaling. In cardiac fibroblasts, HSPA12A promotes USP10-p53 interaction, stabilizing p53 to suppress glycolysis and fibroblast activation. USP10 also regulates metabolism and inflammation through multiple mechanisms, including control of PGK1-dependent glycolytic flux during ischemia–reperfusion, the UBE2S-USP10-GLUT1 axis in metabolic reprogramming and fibrotic signaling, and stabilization of NEMO to promote NF-κB-mediated inflammatory responses. Additionally, TGFβ1-induced stress signaling promotes DAAM1-mediated sequestration and inhibition of USP10 at actin stress fibers, thereby regulating integrin turnover, whereas HSP47-mediated recruitment of USP10 influences SMAD4-dependent profibrotic signaling. TP53, Tumor Protein p53; WT, Wild Type; MT, Mutant; NRF2, Nuclear factor erythroid 2-related factor 2; Keap-1, Kelch-like ECH-associated protein 1; PGK1, Phosphoglycerate kinase 1; RGMA, Repulsive Guidance Molecule-A; UBE2S, Ubiquitin-Conjugating Enzyme E2 S; GLUT1, Glucose Transporter Type 1; TGFβ, Transforming Growth Factor Beta; NEMO, NF-κB Essential Modulator; LPS, Lipopolysaccharide; IKKα, IκB Kinase Alpha; IKKβ, IκB Kinase Beta; IκBα, Inhibitor of Nuclear Factor kappa B Alpha; DAAM1, Disheveled-Associated Activator of Morphogenesis 1; HSP47, Heat Shock Protein 47.

TABLE 2 **Summary of key findings - USP10 pathological roles.**

Disease context	Key findings upon USP10 KD	Mechanism	Perturbation method reported	Level(s) of reported change	Model system	References
Hepatocellular carcinoma (HCC)	Suppression of USP10 by short hairpin RNAs (shRNAs) or Spautin-1 inhibited the migration of HCC cells	Advanced metastasis: stabilization of Smad4 by USP10	USP10 shRNA; Spautin-1 (dual USP10/ USP13 inhibitor)	Protein: Smad4 stabilization; Pathway: downstream signaling not fully specified in table; Functional: cell migration/metastasis	HCC cell lines	[122]
Intrahepatic cholangiocarcinoma (ICC)	USP10 attenuates ICC cell malignancy by deubiquitinating SNAI1	USP10 and snail family transcriptional repressor 1 (SNAI1) reduced the polyubiquitination of the SNAI1 protein and stabilized the SNAI1 protein	USP10 inhibition	Protein: SNAI1 ubiquitination/ stability; Functional: malignancy. mRNA/activity/ localization not specified	RBE cells	[123]
Esophageal cancer (EC)	Activated Wnt/β-Catenin signaling pathway to facilitate ESCC progression	Ubiquitin-specific peptidase 10 (USP10) stabilizes MOF protein by reducing ubiquitination at K410 and inhibiting proteasome-mediated degradation	Si RNA inhibition	Protein: MOF stability/ ubiquitination; Pathway: Wnt/β-catenin	ESCC cell lines, mouse xenograft models	[124]
Esophageal squamous cell carcinoma (ESCC)	USP10 interacts with Anillin (ANLN) and positively regulates ANLN protein levels. Also, integrin β1 and YAP are targets for USP10 deubiquitination	USP10 removes the K11- and K63-linked ubiquitin chains of ANLN, deubiquitinates and stabilizes β1/YAP	macrolide compound FW-04-806 (F806) inhibits USP10	Protein: ANLN, integrin β1 and YAP stability/ deubiquitination; Pathway: YAP-related signaling; Functional: tumor/metastatic phenotypes	ESCC patient samples, ESCC cell lines, mouse xenograft models, metastasis models	[125]
Cutaneous melanoma (CM)	Ubiquitination effect of USP10 and *JPX* on YTHDF2 in cutaneous melanoma, investigating the *JPX*/USP10/YTHDF2/ BMP2 axis	*JPX* can directly interact with YTHDF2 and impede the protection of YTHDF2 from ubiquitin-specific protease 10 (USP10), which promotes its deubiquitination	JPX/USP10 pathway manipulation; exact constructs/reagents not specified in table	Protein: YTHDF2 deubiquitination/ stability; Pathway: BMP2 axis; other levels not specified	Melanoma tissues and cell lines	[126]
Gastric cancer (GC)	LINC00240 (long non-coding RNA) interacts and stabilizes oncoprotein DDX21 by its novel deubiquitinating enzyme USP10,	USP10-DDX21 (oncoprotein) pathway	LINC00240 manipulation; exact USP10 perturbation method not specified in table	Protein: DDX21 stability; Pathway: oncogenic signaling, details not specified	GC cell lines, metastatic tumor models	[127]
Head and Neck squamous cell carcinoma (HNSCC)	OTUB1 expression exhibited a positive correlation with the HNSCC-YAP score in HNSCC cells	OTUB1 in HNSCC progression via modulating YAP1 by USP10	USP10 overexpression/ inhibition	Protein/pathway: YAP1-related signaling; Association: OTUB1 expression versus YAP score. mRNA/protein distinction requires primary-paper verification	Cell lines, male athymic mice	[128]

(*Continued*)

TABLE 2 Continued

Disease context	Key findings upon USP10 KD	Mechanism	Perturbation method reported	Level(s) of reported change	Model system	References
Triple-negative breast cancer (TNBC)	Physical interaction between USP10 and the transcription factor TCF4 causing initiation and tumor progression	TCF4 and USP10 axis	Interaction/functional perturbation details not specified in table; verify primary reference	Protein: physical interaction; Functional: tumor initiation/progression. Direct level of TCF4 regulation not specified	Tumor tissues from patients, cell lines	[129]
Breast cancer (BC)	USP10 bound to and stabilized IGF2BP1 by deubiquitination	USP10/IGF2BP1/CPT1A axis facilitates breast cancer metastasis	USP10 overexpression/inhibition	Protein: IGF2BP1 deubiquitination/stability; Pathway: CPT1A axis; Functional: metastasis	Cell lines and BC mouse models	[130]
Thyroid cancer (THCA)	USP10 mitigated the Erastin-induced ferroptosis in THCA cells, decreased the levels of iron, Fe^{2+}, malondialdehyde, lipid reactive oxygen species, reduced mitochondrial superoxide level, and increased mitochondrial membrane potential	USP10 facilitated the expression of ferroptosis suppressor GPX4 by elevating SIRT6. Loss of USP10 repressed the *in vivo* growth of THCA cells. GPX4-SIRT6-USP10 axis	USP10 loss/perturbation; erastin-induced ferroptosis model	Protein: SIRT6/GPX4-associated effects; Pathway: ferroptosis suppression; Functional: lipid peroxidation, ROS, mitochondrial potential and tumor growth. Transcript-level changes not specified	Human THCA cell lines, ferroptosis induction model, mouse xenograft model	[131]
Pancreatic cancer (PC)	LINC00460 was upregulated in pancreatic cancer cells and tissues	LINC00460 promotes pancreatic cancer development by sequestering USP10, a that deubiquitinates p53 and enhances its stability	Inhibition of LINC00460 and over-expression	mRNA: LINC00460 expression; Protein: p53 stability; Pathway: p53 signaling; Functional: tumor development	Human cancer cell lines, mouse xenograft model	[132]
Pancreatic ductal adenocarcinoma (PDAC)	USP10 decreased the K27/29-linked ubiquitination level of the RRM2 domain of PABPC1	Deubiquitinated PABPC1 binds more CLK2 mRNA and eIF4G1, which increases the translation efficiency of CLK2 mRNA	Replacing PABPC1 with a mutant/USP10 knockdown	Protein: PABPC1 ubiquitination; mRNA/translation: CLK2 mRNA binding/translation efficiency; Pathway: translation control	Human bladder cancer cell lines, mouse xenograft model	[133]
Endometriosis (EM)	USP10 was upregulated in EM and associated with increased ERK1/2 activation, inflammation, and anti-apoptotic signaling (↑Bcl-2, ↓Bax, ↓Caspase-7). CNYP (Cai's Neiyi Prescription) treatment inhibited USP10, promoting apoptosis and reducing inflammatory cytokines. USP10 overexpression reversed, while USP10 siRNA enhanced, the anti-inflammatory and pro-apoptotic effects of CNYP.	CNYP suppresses USP10/ERK1/2 signaling, shifting the balance toward apoptosis and dampening inflammation in endometrial stromal cells	CNYP treatment; USP10 overexpression; USP10 siRNA.	Protein/pathway: ERK1/2 activation and Bcl-2/Bax/caspase-7 changes (assay level to verify); Functional: apoptosis/inflammation; expression level of USP10 not specified as mRNA or protein	Patient stromal cells	[134]

(*Continued*)

TABLE 2 Continued

Disease context	Key findings upon USP10 KD	Mechanism	Perturbation method reported	Level(s) of reported change	Model system	References
Dilated cardiomyopathy (DCM)	USP10 promoted EndMT by mediating Smad4 deubiquitination, contributing to cardiac dysfunction and remodeling. EDIL3 deficiency or USP10 inhibition attenuated EndMT and improved cardiac function. Recombinant EDIL3 aggravated EndMT through USP10-dependent Smad4 stabilization	EDIL3-USP10-Smad4 axis: EDIL3 upregulates USP10, which deubiquitinates and stabilizes Smad4, enhancing TGF-β/Smad signaling and driving EndMT and DCM progression	EDIL3 deficiency; USP10 inhibition; recombinant EDIL3	Protein: Smad4 deubiquitination/ stability; Pathway: TGF-β/ Smad; Functional: EndMT and cardiac function	DCM mouse models, human umbilical vein endothelial cells	[135]
Myocardial ischemia–reperfusion injury (IRI) and post-infarction cardiac remodeling	Cardiac fibroblast-selective HSP47 overexpression elevated fibrosis and cardiac dysfunction after IRI. HSP47 promoted Smad4 deubiquitination and activation by recruiting USP10. USP10 deficiency in cardiac fibroblasts abolished HSP47-mediated fibrogenesis. Inhibition of HSP47 (Col003) suppressed fibroblast fibrogenesis and TGFβ1-Smad4 signaling	HSP47USP10-Smad4 axis: HSP47 recruits USP10 to deubiquitinate and stabilize Smad4, enhancing TGFβ1/Smad signaling and fibrogenesis during myocardial IRI and remodeling	Cardiac fibroblast-selective HSP47 overexpression; USP10 deficiency; HSP47 inhibitor Col003	Protein: Smad4 deubiquitination/ stability; Pathway: TGF-β1/ Smad; Functional: fibrosis and cardiac dysfunction	Human heart samples, myocardial IRI mouse model, mouse cardiac fibroblasts	[136]
Acute Lung Injury (ALI)	Spautin-1, a dual inhibitor of USP10/USP13, significantly reduced lung injury, inflammation, epithelial necroptosis, and apoptosis in LPS-induced ALI, but not in bleomycin-induced injury. It also mitigated oxidative stress damage in lung epithelial cells	Inhibition of USP10/ 13 led to suppression of NF-κB signaling in leukocytes, decreased autophagy in immune and epithelial cells, and protection against oxidative stress–mediated injury	Spautin-1; LPS-induced and bleomycin injury models	Pathway: NF-κB/autophagy; Functional: inflammation, necroptosis, apoptosis and oxidative injury. Enzyme-specific attribution limited because Spautin-1 inhibits USP10/USP13	LPS-induced ALI mouse model, LPS-stimulated neutrophils	[137]
Sepsis/LPS-induced systemic inflammation	USP10 expression was upregulated following LPS stimulation. USP10 inhibition (Spautin-1 or siRNA) reduced TNF-α and IL-6 levels, decreased NF-κB activation, and improved survival in septic mice	USP10 stabilizes NEMO (NF-κB essential modulator) by deubiquitination and promotes NF-κB translocation and pro-inflammatory cytokine production. Inhibiting USP10 accelerates NEMO degradation which suppresses NF-κB signaling and systemic inflammation	Spautin-1; USP10 siRNA; LPS stimulation	Protein: NEMO deubiquitination/stability; Pathway: NF-κB; Functional: cytokine production and survival	LPS-induced mouse sepsis model, LPS-stimulated macrophages	[138]

(*Continued*)

TABLE 2 Continued

Disease context	Key findings upon USP10 KD	Mechanism	Perturbation method reported	Level(s) of reported change	Model system	References
Amyotrophic Lateral Sclerosis (ALS)	lncRNA NR3C2-8:1 (Lnc-NR3C) was decreased in ALS patients. Lnc-NR3C promotes p53-mediated neuronal apoptosis by upregulating USP10, leading to p53 activation and oxidative stress–induced cell death. Knockdown of lnc-NR3C suppressed USP10-triggered p53 activation and protected cells	Lnc-NR3C/miR-129-5p/USP10/p53 axis: Lnc-NR3C acts as a ceRNA, sequestering miR-129-5p which increases USP10; stabilizes and activates p53, triggering apoptosis	Lnc-NR3C knockdown; manipulation of lncRNA/miRNA axis (specific details not fully stated in table)	mRNA/noncoding RNA: lnc-NR3C and miR-129-5p axis; Protein: USP10/p53 stabilization/activation; Pathway: p53; Functional: apoptosis/oxidative stress	Human cell lines, peripheral blood samples, brain tissue samples	[139]
Keloid formation/fibrotic skin disorder	TRAF4 overexpression in keloid fibroblasts suppresses p53 signaling and promotes fibroblast proliferation by interfering with USP10-p53 interaction. TRAF4 binds USP10, preventing USP10 from deubiquitinating and stabilizing p53, leading to p53 destabilization	TRAF4/USP10/p53 axis: TRAF4 sequesters USP10, blocks USP10-mediated p53 stabilization, reduces p53-p21 pathway activity thereby excessive fibroblast proliferation. TRAF4 knockdown restores p53 activity and suppresses fibroproliferation	TRAF4 overexpression/knockdown	Protein: USP10–p53 interaction and p53 stability; Pathway: p53–p21; Functional: fibroblast proliferation	Normal and keloid fibroblast cultures	[140]
Corneal Fibrosis/scarring	USP10 is upregulated in fibrotic myofibroblasts. Silencing USP10 led to accumulation of ubiquitinated β1 and β5 integrins thereby decreased αv/β1/β5 protein levels; reduced TGFβ activation; suppression of α-SMA and FN-EDA. Overexpression of USP10 had the opposite effect, promoting fibrosis	USP10 deubiquitinates integrin β1 and β5, stabilizing them on the cell surface	USP10 silencing and overexpression	Protein: integrin β1/β5 stability; Subcellular localization: cell-surface integrins; Pathway: TGF-β; Functional: α-SMA/FN-EDA and fibrotic phenotype	Human corneal fibroblasts, porcine organ culture	[141]

USP10 and Wnt/β-catenin pathway

USP10 promotes tumor growth in colorectal cancer through β-catenin stabilization. Riessland et al. showed that USP10 stabilizes β-catenin in tumors with truncated Adenomatous Polyposis Coli (APC) protein [142]. In normal epithelial cells, intact APC preferentially binds β-catenin over USP10, resulting in proteasomal degradation and dysregulated Wnt signaling, preventing tumorigenesis. However, truncated APC preferentially binds to USP10 over β-catenin via its unstructured N-terminus, increasing β-catenin stability and sustaining Wnt activation, promoting tumor growth. In murine and patient-derived colorectal cancer organoids, USP10 silencing reduced Wnt and stemness signatures, impaired activity of NOTUM (a secreted Wnt antagonist that acts as a feedback regulator of Wnt signaling) and decreased tumorigenicity. Clinically, high USP10 expression correlated with poor prognosis. These findings indicate that in APC-deficient colorectal cancer, USP10 promotes tumor progression by stabilizing β-catenin and maintaining elevated Wnt signaling [142].

The opposing effects of USP10 in cancer can similarly be interpreted through the identity and functional state of its substrates rather than through USP10 abundance alone. Stabilization of wild-type p53 can restrict tumor growth, whereas stabilization of oncogenic signaling components such as β-catenin [142], YAP/TAZ [143], SMAD4 [122], EIF4G1 [144], or

G3BP2 [120, 121] can support proliferation, survival, invasion, or metabolic adaptation. Importantly, these outcomes are also influenced by tumor genotype. The APC-deficient colorectal cancer setting provides an example in which loss of normal APC-mediated β-catenin regulation alters the competitive interaction between APC, β-catenin, and USP10, favoring β-catenin stabilization [142]. Similarly, the consequences of USP10 activity in tumors retaining functional p53 may differ from those in tumors in which p53 is mutated, deleted, or functionally suppressed. Consequently, USP10 expression should not be interpreted as a universal biomarker of either tumor suppression or tumor promotion without considering the underlying genetic background and dominant substrate network.

USP10 and deacetylation pathway

USP10 also regulates cancer progression through interaction with HDAC6, a class IIb histone deacetylase overexpressed in various cancers, including gastric cancer, glioblastoma, melanoma, and non-small cell lung cancer (NSCLC) [145–157]. HDAC6 serves as a master regulator of proteotoxic, endoplasmic reticulum (ER), and genotoxic stress responses and plays a part in chemoresistance across various tumor types [148, 149, 154, 158]. HDAC6 also exhibits E3 ubiquitin ligase activity toward key DNA damage response proteins, including MutS Homolog 2 (MSH2) and Checkpoint kinase 1 (CHK1), thereby modulating mismatch repair and ATR/CHK1 signaling [145, 159]. USP10-mediated deubiquitination stabilizes HDAC6, linking its activity to cellular stress and DNA damage response pathways. The stabilization of HDAC6 via USP10 supports tumor cell survival [156, 160, 161].

USP10 and post-transcriptional/translational control

In NSCLC, this signaling is achieved through stabilization of multiple complementary factors like eukaryotic translation initiation factor 4 gamma (EIF4G1) and Insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) that collectively support malignant growth. USP10 stabilizes the translation initiation factor EIF4G1, thereby upregulating protein synthesis that drives proliferation, migration, and invasion [144]. In parallel, USP10 stabilizes the RNA-binding protein IGF2BP3, sustaining S-phase kinase-associated protein (SKP2) expression and promoting cell cycle progression and tumor growth [162, 163]. These findings position USP10 as an important regulator of translational (via stabilizing EIF4G1) and post-transcriptional (via stabilizing IGF2BP3) control in promoting NSCLC [163].

USP10 and therapy resistance development in cancer

USP10 promotes cancer stemness and therapeutic resistance across multiple tumor types. In breast cancer, USP10 stabilizes CD44, activating Ezrin/Radixin/Moesin (ERM; cytoskeletal linker proteins that connect membrane receptors to the actin cytoskeleton) and platelet-derived growth factor receptor β/signal transducer and activator of transcription-3 (PDGFRβ/STAT3) pathways that drive stemness, metastasis, and chemoresistance [164]. Similarly, in HNSCC (Head and Neck Squamous Cell Carcinoma), USP10 stabilizes bromodomain adjacent to zinc finger domain 1A (BAZ1A), enabling SOX2-dependent transcriptional reprogramming (a stemness-associated transcription factor network that maintains self-renewal) and promoting resistance to cisplatin [165]. These findings indicate that USP10 stabilizes key regulators of cellular plasticity, thereby enhancing survival and therapy resistance in malignant cells.

USP10 in oncogenic signaling across cancer types

USP10 also drives tumor progression across diverse biological processes, including signal transduction, metabolism, and epigenetic regulation. In hepatocellular carcinoma (HCC), USP10 stabilizes the tumor suppressor Smad4, sustaining TGF-β signaling (which regulates proliferation, epithelial-mesenchymal transition, and metastasis) and promoting metastatic progression [122]. In thyroid cancer, USP10 suppresses ferroptosis (iron-dependent lipid peroxidation–mediated cell death) by stabilizing the stress response protein SIRT6 and activating the lipid peroxide detoxifying enzyme GPX4, conferring resistance to this form of cell death [131]. In pancreatic ductal adenocarcinoma (PDAC), USP10 supports tumor survival under adverse microenvironmental conditions by stabilizing Poly(A)-Binding Protein Cytoplasmic 1 (PABPC1) to enhance translation (mRNA stability and protein synthesis), as well as phosphoglycerate kinase 1 (PGK1; one of the key enzymes in glycolysis) to sustain glycolysis (ATP generation from glucose), and by attenuating ER stress responses (stress caused by misfolded proteins) [133, 166, 167]. Similarly, USP10 stabilizes Yes-associated protein 1 (YAP1; Hippo pathway transcriptional co-activator) in osteosarcoma [168],Runt-related transcription factor 1 (RUNX1; lineage-specific transcription factor) in mesenchymal glioblastoma [169], cyclin D3 (CCND3; cell cycle regulator) in multiple myeloma [170], and MOF (histone acetyltransferase) in esophageal squamous cell carcinoma (ESCC), where it enhances Wnt/β-catenin signaling through increased acetylation of the histone H4K16 (epigenetic activation) [124]. Together, these findings highlight USP10 as a central oncogenic driver, independent of p53 signaling, across multiple pathways, enabling tumor cells to maintain transcriptional programs, metabolic and stress adaptation, and therapy resistance.

The major USP10 substrates and their associated functional outcomes across different malignancies are summarized in Table 3.

Pathological role of USP10 in AMPK signaling in cancer

Contrary to the USP10/AMPK axis limiting CRC progression as mentioned earlier in the protective scope, it also supports oncogenic survival in hematologic malignancies. For instance, in acute myeloid leukemia (AML), USP10/AMPK signaling activates oncogenic programs. Yu et al. identified USP10 as a critical stabilizer of the mutant receptor tyrosine kinase FLT3 internal tandem duplication (FLT3-ITD), associated with poor prognosis and resistance to therapy. The pharmacological inhibitor of USP10, Wu-5, induced proteasome-dependent degradation of FLT3-ITD in both FLT3 inhibitor–sensitive and resistant AML cell lines, resulting in dose-dependent apoptosis. Overexpression of USP10 reversed these

effects, confirming specificity [171]. Wu-5 synergizes with the FLT3 inhibitor crenolanib, enhancing cytotoxicity and reducing FLT3 and AMPKα protein levels. These results indicate that in AML, USP10 stabilizes both FLT3-ITD and AMPKα to support leukemic cell survival, and that USP10 inhibition can overcome resistance to FLT3-targeted therapy [171].

Pathological role of USP10 in non-malignant conditions

Outside the cancer paradigm, USP10 stabilizes metabolic and signaling proteins that regulate both glycolytic metabolism and pro-inflammatory pathways, thereby impairing tissue recovery. USP10 plays deleterious roles in neurons by driving harmful metabolic changes after ischemic injury. With context to glycolysis, in an ischemia-reperfusion (I/R) injury, USP10 promotes neuronal glycolysis by stabilizing PGK1 [172]. This is crucial because after ischemic insult, Wang et al. showed that induction of repulsive guidance molecule-A (RGMA), enhances USP10-mediated deubiquitination of PGK1, increasing glycolytic flux. Disruption of RGMA reduces USP10/PGK1 binding, destabilizes PGK1, and redirects neuronal metabolism toward oxidative phosphorylation, thereby reducing oxidative damage and improving overall neuronal survival. Sustained USP10-driven glycolysis can worsen neuronal injury following ischemic stress (Figure 4B) [172]. In chronic inflammatory conditions such as endometriosis, USP10 sustains high glycolytic activity and lactate accumulation in ectopic endometrial stromal cells. In parallel, Wang et al. also reported that ubiquitin-conjugating enzyme E2S (UBE2S) interacts with USP10 and Glucose Transporter Type 1 (GLUT1), promoting USP10-dependent deubiquitination and stabilization of GLUT1, thereby maintaining elevated glycolysis and local tissue acidification and linking USP10 activity to chronic inflammation and tissue remodeling (Figure 4B) [173].

Pathological role of USP10 in fibrosis

Beyond its established roles in tumor progression, USP10 also contributes to pathological tissue remodeling by regulating conserved fibrotic programs, including TGF-β activation, integrin signaling, ECM organization, and myofibroblast differentiation, like in eyes and heart. In the ocular context, corneal wound healing models provide an excellent mechanistic framework for USP10-mediated fibrosis [141, 174]. USP10 promotes fibrotic remodeling by stabilizing key proteins that drive myofibroblast differentiation during healing. USP10 is upregulated in corneal fibroblasts after wounding and TGF-β stimulation where it directly removes ubiquitin from the β subunits of αvβ1 and αvβ5 integrins, preventing degradation and stabilizing αv integrins at the cell surface. This promotes latent TGF-β activation and induces fibrotic markers including fibronectin-EDA and α-SMA characteristic of myofibroblast differentiation. USP10 also promotes fibronectin recycling and secretion through enhanced recycling of α5β1 and αv integrins, which govern fibronectin uptake and redeposition, resulting in denser and more organized fibronectin fibrils. By stabilizing integrins and increasing fibronectin trafficking, USP10 mediates a feed-forward loop linking integrin signaling, ECM stiffening, and sustained TGF-β activation [175]. siRNA knockdown of USP10 reduces integrin abundance and fibrotic scarring in an *ex vivo* cornea model, suggesting that USP10 inhibition can direct wound healing toward regenerative outcomes [176]. USP10 activity is dynamically regulated by protein partners (Figure 4B). Disheveled Associated Activator of Morphogenesis 1 (DAAM1) is an upstream regulator that binds USP10 and directly inhibits its deubiquitinase activity. DAAM1 knockdown increased integrin recycling and ECM deposition; USP10 knockdown reversed these effects, confirming that DAAM1 regulates fibrosis through the USP10/integrin axis [177]. Therapeutic silencing studies of USP10 *in vivo* and *ex vivo* [178] further supports its pathogenic role in scarring. A single topical dose of a chemically stabilized, self-delivering siRNA (sdRNA) targeting USP10 reduced fibrosis, immune infiltration, and preserved tissue architecture in a rabbit corneal wound model [174]. In a mouse persistent corneal epithelial defect model, USP10 silencing improved epithelial wound closure, restored basement membrane integrity, suppressed fibrotic markers, and reduced immune infiltration [179]. Transcriptomic analysis revealed suppression of ECM deposition and integrin signaling with activation of proliferation and DNA repair pathways, supporting a model in which USP10 knockdown disrupts the fibrotic loop and promotes regenerative healing [141, 174, 175, 179].

USP10 also participates in pathological scar formation in keloids through regulation of the TRAF4–p53 axis. In keloid fibroblasts, elevated TRAF4 interacts with USP10 and prevents USP10-mediated stabilization of p53, resulting in reduced p53–p21 signaling and enhanced fibroblast proliferation. Disruption of TRAF4 restores USP10–p53 interaction and suppresses the proliferative phenotype of keloid fibroblasts. These findings highlight another mechanism by which altered USP10 substrate interactions can shift tissue repair toward pathological fibrosis [140].

Similar to corneal fibrosis, USP10 also promotes pathological cardiac remodeling by stabilizing key mediators of TGF-β signaling. USP10 functions as a downstream effector of EGF-like repeat and discoidin I-like domain-containing protein 3 (EDIL3)-driven endothelial-to-mesenchymal transition (EndMT) in dilated cardiomyopathy. EDIL3, an extracellular matrix glycoprotein, enhances USP10-mediated deubiquitination and stabilization of Smad4, thereby amplifying TGF-β signaling and promoting EndMT. Genetic deletion of EDIL3 or pharmacological inhibition of USP10 attenuates EndMT and improves cardiac function, highlighting the EDIL3/USP10/Smad4 axis as a driver of pathological remodeling [135]. Interestingly, a similar Smad4-dependent mechanism operates during myocardial ischemia-reperfusion injury, where heat shock protein 47 (HSP47) upregulation recruits USP10 to stabilize Smad4 and enhance TGF-β1-mediated fibrotic signaling. Fibroblast-specific deletion of USP10 prevents HSP47-induced fibrosis, further establishing Smad4 stabilization as a recurring mechanism through which USP10 promotes cardiac fibrosis [136]. Together, these studies identify USP10 as a conserved amplifier of profibrotic TGF-β signaling across distinct cardiac injury contexts.

Pathological role of USP10 in mechanotransduction

Mechanical inputs regulate YAP/TAZ activity, two mechanosensitive transcriptional coactivators, primarily through

TABLE 3 USP10-mediated oncogenic mechanisms across cancer types.

Cancer type	USP10 target(s)	Pathway affected	Functional outcomes	References
Hepatocellular carcinoma (HCC)	Smad4	TGF-β signaling, EMT, metastasis	Promotes metastatic progression	[122]
Thyroid cancer (THCA)	SIRT6, GPX4	Ferroptosis resistance (lipid peroxide detoxification)	Enhances cancer cell survival under oxidative stress	[131]
Pancreatic ductal adenocarcinoma (PDAC)	PABPC1, PGK1	Translation control, glycolysis, ER stress response	Metabolic adaptation and tumor survival	[133]
Osteosarcoma (OS)	YAP1	Hippo signaling	Promotes oncogenic transcription and growth	[168]
Glioblastoma (GBM) (mesenchymal subtype)	RUNX1	Transcriptional regulation	Maintains malignant gene expression programs	[169]
Multiple myeloma (MM)	CCND3	Cell cycle progression	Promotes proliferation	[170]
Esophageal squamous cell carcinoma (ESCC)	MOF	Histone acetylation (H4K16ac), Wnt/β-catenin signaling	Epigenetic activation of oncogenic transcription	[124]

modulation of the Hippo kinase cascade [180]. Under high mechanical stress or increased ECM stiffness, suppression of upstream kinase activity (MST/LATS) permits YAP/TAZ nuclear translocation and TEAD-dependent transcription of genes controlling proliferation, survival, migration, and ECM remodeling. Conversely, Hippo pathway activation promotes YAP/TAZ phosphorylation, cytoplasmic retention, and degradation [181, 182]. The canonical regulation of YAP/TAZ activity through upstream mechanical and biochemical inputs is illustrated in Figure 5A.

Although mechanical regulation of YAP/TAZ has traditionally been attributed to phosphorylation-dependent Hippo signaling, increasing evidence indicates that YAP/TAZ protein stability is also controlled by ubiquitination dynamics. Within this framework, USP10 has emerged as a key deubiquitinase that regulates YAP/TAZ activity by modulating their proteasomal degradation. USP10 directly binds YAP and TAZ, removes polyubiquitin chains, and prevents their degradation, thereby sustaining YAP/TAZ protein stability and downstream transcriptional activity. Functional studies demonstrate that USP10 depletion reduces YAP/TAZ abundance and attenuates transcriptional programs associated with proliferation, migration, and cellular plasticity (Figure 5B). Consistently, *in vivo* models of pathological tissue remodeling show coordinated upregulation of USP10 and YAP/TAZ, supporting a role for USP10 in amplifying mechanotransduction signaling outputs [143, 168].

Beyond direct regulation of YAP/TAZ, USP10 also reinforces mechanotransduction through adhesion-dependent signaling pathways. Integrin β1-mediated adhesion promotes YAP activation in part by suppressing its phosphorylation and facilitating nuclear activity [183]. In this context, USP10 stabilizes both YAP and integrin β1 through deubiquitination, thereby strengthening adhesion signaling and reinforcing mechanically driven transcriptional responses. This coordinated regulation links ECM-integrin interactions to sustained YAP/TAZ activation and downstream gene programs involved in cellular migration, plasticity, and extracellular matrix remodeling. Evidence for this mechanism is supported across multiple pathological contexts. In hepatocellular carcinoma, esophageal squamous cell carcinoma, and osteosarcoma, elevated USP10 expression correlates with increased YAP/TAZ activity and enhanced proliferative and migratory phenotypes. Functional studies further demonstrate that USP10 binds YAP/TAZ, removes polyubiquitin chains, and prevents proteasomal degradation, whereas USP10 depletion suppresses YAP/TAZ-dependent transcription, reduces tumor growth, and impairs metastatic potential [143]. These findings collectively support a conserved role for USP10 in sustaining YAP/TAZ-driven mechanotransduction programs across diverse disease contexts.

Pathological role of USP10 in inflammation

Inflammation is a protective biological response that eliminates pathogens and initiates tissue repair [184]. However, its persistence can transition into a pathological state that drives tissue injury causing diseases such as sepsis, atherosclerosis, cancer, and fibrosis. Studies demonstrate that USP10 promotes inflammation by stabilizing key signaling proteins across multiple pathways. A central pro-inflammatory mechanism of USP10 involves amplification of NF-κB signaling [138]. During LPS-induced immune activation, USP10 stabilizes NEMO, promoting NF-κB-dependent transcription of inflammatory cytokines, including TNF-α and IL-6 (Figure 4B). This mechanism contributes to the inflammatory response during endotoxemia, a condition associated with the systemic presence of bacterial endotoxins. Consistent with this role, genetic or pharmacological inhibition of USP10 has been shown to reduce inflammatory cytokine production and improve survival in experimental sepsis models. Furthermore, Wen et al. showed that USP10 inhibition with Spautin-1 (a non-selective USP10 inhibitor) reduces macrophage and neutrophil NF-κB activation and attenuates inflammatory injury in sepsis and acute lung injury models [137]. In chronic inflammatory diseases like atherosclerosis, Xia et al. showed that USP10 stabilizes CD36, enhancing oxidized low-density lipoprotein (oxLDL) uptake and macrophage foam-cell formation, whereas its deletion suppresses lipid-driven inflammation [185]. In vascular

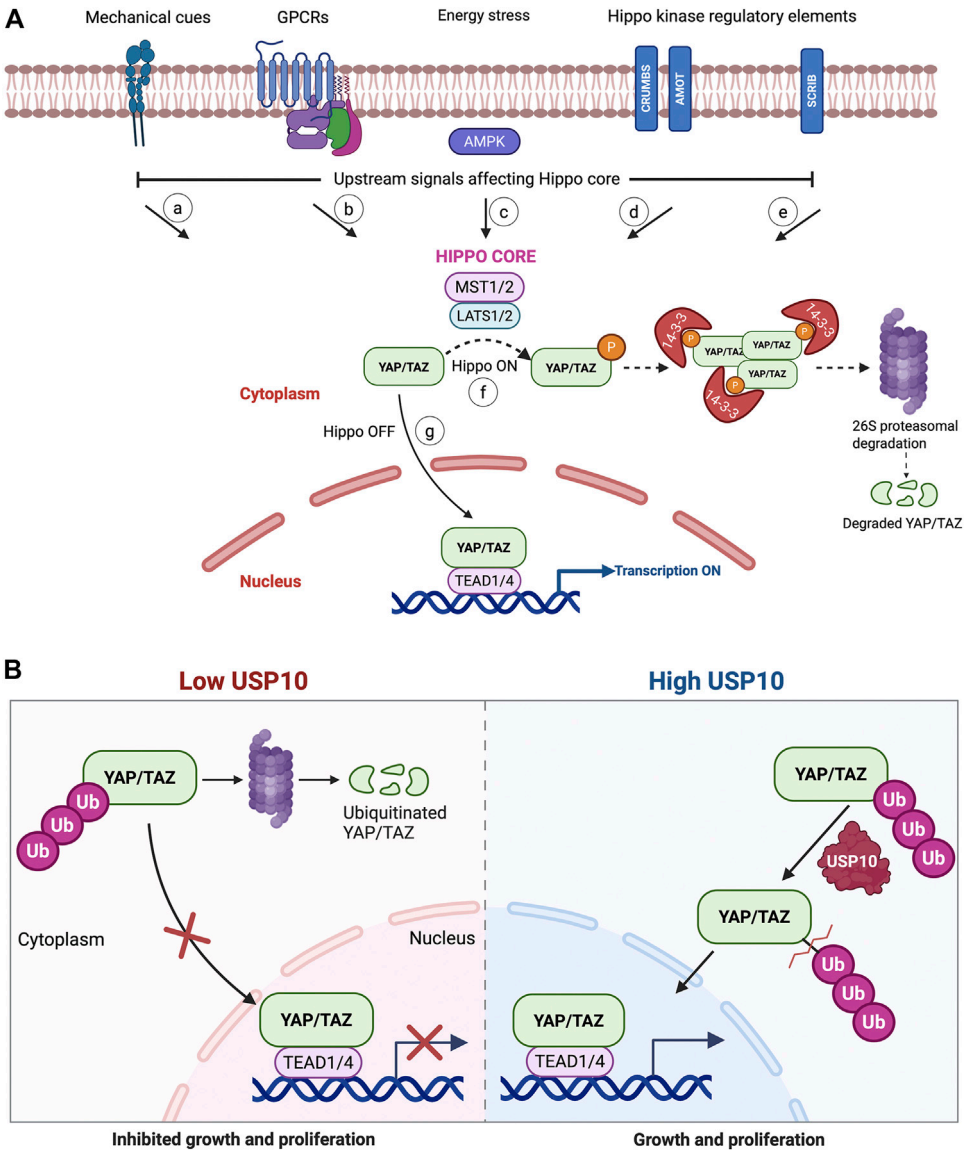


FIGURE 5
Schematic representation of the Hippo/YAP/TAZ-TEAD signaling pathway and USP10-mediated regulation. **(A)** Multiple upstream cues regulate the Hippo kinase cascade and YAP/TAZ signaling. **(a)** Mechanical cues, including ECM stiffness, cell-cell contact, cytoskeletal tension, and mechanical forces, regulate Hippo pathway activity. **(b)** GPCR signaling, activated by ligands such as lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P), modulates YAP/TAZ signaling in a ligand- and receptor-dependent manner. **(c)** Energy stress, sensed through AMPK, generally restricts YAP nuclear activity and promotes its cytoplasmic retention. **(d,e)** Polarity-associated proteins, including CRUMBS, AMOT, and SCRIB, transmit upstream signals to the Hippo core kinase complex. **(f)** When Hippo kinases (MST1/2-LATS1/2) are active, YAP becomes phosphorylated at Ser127 and TAZ at Ser89, which promotes binding to 14-3-3 proteins and leads to cytoplasmic sequestration. Phosphorylated YAP/TAZ and the 14-3-3 complex are recognized by the E3 ubiquitin ligase and targeted for ubiquitin-mediated proteasomal degradation, thereby suppressing their transcriptional activity. On the other hand, when Hippo kinase activity is suppressed, YAP/TAZ becomes dephosphorylated, translocates to the nucleus, and associates with TEAD transcription factors to activate gene expression programs driving proliferation, survival, and migration. **(B)** USP10 regulates YAP/TAZ protein stability through its deubiquitinating activity. Under low USP10 levels, ubiquitinated YAP/TAZ undergos proteasomal degradation, reducing transcriptional activation and inhibiting cell growth and proliferation. In contrast, high USP10 levels promote deubiquitination and stabilization of YAP/TAZ, allowing their nuclear localization and interaction with TEAD transcription factors to enhance gene expression associated with cellular growth and proliferation. GPCR, G-Protein-Coupled Receptor; CRUMBS, Crumbs Cell Polarity Complex Component; AMOT, Angiomotin; SCRIB, Scribble Planar Cell Polarity Protein; MST1/2, Mammalian Sterile 20-like Kinases 1 and 2; LATS1/2, Large Tumor suppressor kinases 1 and 2; YAP, Yes-associated Protein; TAZ, Transcriptional Co-activator with PDZ-binding Motif (WWTR1); TEAD, TEA Domain Transcription Factor.

smooth muscle cells, the long non-coding RNA INKILN scaffolds USP10 with MKL1 to drive inflammatory gene expression programs associated with vascular remodeling and disease progression [186]. USP10 also modulates inflammatory microenvironments by controlling immune-cell recruitment and polarization. In colorectal cancer, USP10-mediated stabilization of NLR family pyrin domain containing 7 (NLRP7) enhances NF-κB-C-C motif chemokine ligand 2 (CCL2) signaling, promoting tumor-associated macrophage recruitment and polarization [187]. In parallel, USP10 contributes to inflammasome activation through a

S100 calcium-binding protein A9 (S100A9)-spleen tyrosine kinase (SYK)-NOD-like receptor family pyrin domain containing 3 (NLRP3) axis, driving caspase-1 activation, gasdermin D (GSDMD) cleavage, and pyroptotic cytokine release [188]. In metabolic-inflammatory disorders, USP10 links immune activation with metabolic and fibrotic reprogramming. In endometriosis, a UBE2S-USP10-GLUT1 axis promotes glycolytic reprogramming, M2 macrophage polarization, TGF-β1 signaling, and fibrosis, while USP10 inhibition reduces inflammatory responses in stromal cells [173]. Collectively, USP10 emerges as a major pro-inflammatory DUB driving pathological inflammation across multiple signaling and disease contexts.

Pathological role of USP10 in mitochondrial regulation

Taking into consideration the protective role of USP10 in mammalian mitochondrial dynamics, studies in yeast have revealed a pathological role for the USP10 homolog Ubp3 in regulating cellular metabolism and mitochondrial respiration in response to nutrient availability [189]. Under glucose-rich conditions, Ubp3 contributes to repression of mitochondrial respiration, thereby favoring glycolytic metabolism. Genetic loss of Ubp3 relieves this glucose-induced suppression, resulting in reduced glycolytic flux and a metabolic shift that enhances mitochondrial respiratory activity and oxidative phosphorylation. This indicates that Ubp3 functions as a regulatory node in coordinating the balance between glycolysis and mitochondrial respiration depending on nutrient status. Mechanistically, Ubp3 deficiency alters intracellular metabolic fluxes that increases inorganic phosphate availability, which further supports mitochondrial respiratory activity. Through this process, Ubp3 influences the partitioning of glucose-derived metabolites between glycolytic and oxidative pathways, thereby shaping overall cellular energy homeostasis [189].

The yeast Ubp3 findings provide useful evolutionary evidence that USP10-family DUBs can participate in nutrient-sensitive regulation of cellular metabolism, but they should not be interpreted as direct evidence that mammalian USP10 produces the same mitochondrial phenotype. Ubp3 and mammalian USP10 share evolutionary relationships, yet their substrate repertoires, interacting partners, regulatory mechanisms, and cellular environments are not necessarily equivalent. Therefore, the Ubp3 observations are best considered a hypothesis-generating framework suggesting that USP10-family enzymes may couple ubiquitin signaling to metabolic state [189]. In mammals, the direct evidence currently supports protective roles for USP10 in mitochondrial homeostasis through substrates such as Mfn2 [114] and YBX1, whereas a pathological mitochondrial role for mammalian USP10 remains less firmly established. Determining whether mammalian USP10 directly regulates nutrient-dependent partitioning between glycolysis and oxidative phosphorylation, as observed for Ubp3, will require substrate-specific biochemical studies and mammalian genetic models.

Emerging therapies targeting USP10

The recognition of the pathological roles of USP10 in stress signaling, oncogenic protein stability, and fibrosis has prompted the exploration of diverse preclinical and proof-of-concept therapeutic strategies aimed at modulating its activity. These approaches include small-molecule DUB inhibitors [171, 190–195], RNA interference-based silencing [174, 179, 196], peptide disruptors [197], and emerging targeted protein degradation strategies. However, these modalities remain at the experimental stage, with evidence derived from *in vitro* systems and *in vivo* animal models, as no USP10-specific therapy has reached clinical application or FDA approval. Accordingly, while modulation of USP10 signaling represents a mechanistically promising therapeutic avenue, challenges still remain in achieving selective, context-dependent, and clinically translatable therapeutic strategies that preserve the physiological functions of USP10 across different cellular settings. Representative experimental (preclinical and proof-of-concept) strategies targeting USP10 are summarized in Table 4.

Although most USP10-targeted strategies focus on inhibition, preserving or restoring USP10 activity may be beneficial in diseases involving impaired stress responses, metabolic adaptation, autophagy, antioxidant defense, or mitochondrial quality control. Protective effects have been reported in preclinical models of pulmonary fibrosis, metabolic liver disease, cardiac hypertrophy, and ischemic injury [24, 86–88, 105, 114, 116]. Therapeutic approaches could therefore include restoring protective USP10–substrate interactions in disease-relevant cells. Thus, USP10-directed therapy should be tailored to the dominant substrate network and cellular context to maximize therapeutic benefit while minimizing disruption of its physiological functions.

Discussion

Determinants of USP10 substrate specificity

The broad and functionally diverse substrate repertoire attributed to USP10 raises a fundamental mechanistic question: how can a single deubiquitinase produce distinct biological outcomes across different cellular and disease contexts? The available evidence suggests that USP10 specificity is unlikely to be governed solely by the catalytic domain. Rather, substrate engagement appears to emerge from the integration of several determinants, including substrate abundance and ubiquitination state, USP10 localization and activation, adaptor or scaffold interactions, and the structural features of the ubiquitin modification itself [199]. Together, these factors may define which substrates are accessible to USP10 and which interactions result in productive deubiquitination (Figure 6).

The first determinant is the availability and ubiquitination state of the substrate. Productive deubiquitination requires not only the presence of a potential substrate but also an appropriate ubiquitination state. Importantly, the functional consequence of USP10 activity may differ according to the ubiquitin linkage being removed. Removal of K48-linked ubiquitin can stabilize substrates by limiting proteasomal degradation, whereas deubiquitination of non-proteolytic ubiquitin chains can regulate protein activity, localization, or signaling without necessarily altering protein abundance [42]. The USP10–AMPK axis illustrates this distinction, in which USP10 removes K63-linked ubiquitination from AMPKα and promotes its activation rather than simply

TABLE 4 Experimental and preclinical strategies targeting USP10 across disease models and mechanistic contexts.

Compound/ strategy	Specificity	Evidence level	Model system/ delivery approach	On-target validation	Outcomes	References
Spautin-1	USP10/USP13 dual inhibitor	Experimental tool compound; preclinical therapeutic evaluation	Murine unilateral ureteral obstruction (UUO) fibrosis model; chronic myeloid leukemia, ovarian cancer, lung cancer, melanoma models; small molecule administration	Partial validation through USP10/USP13 inhibition, Beclin-1 destabilization, and downstream pathway modulation	Reduces renal fibrosis, tubular atrophy, ECM deposition, and profibrotic gene expression (Fn1, Acta2, Col1a1, Col3a1); suppresses PI3K/AKT signaling; destabilizes MCL1; activates p53-dependent DNA damage response pathways	[190, 191]
HBX19818	USP10/USP7 dual inhibitor	Early pharmacological validation	AML models (Ba/F3-FLT3-ITD, MOLM13, MOLM14), SYK-TEL B-cell leukemia models; human leukemia cell lines; PBMCs from healthy donors; *in vitro* + *in vivo* xenograft studies; small-molecule systemic treatment	Biochemical DUB inhibition assays; functional loss-of-target studies; downstream pathway readouts; correlation between USP10 inhibition and SYK/FLT3 protein stability	Treatment results in reduction of SYK and FLT3 protein levels in leukemia models; suppression of downstream oncogenic signaling pathways; inhibition of leukemia cell proliferation; enhancement of sensitivity to FLT3-targeted therapies in AML models	[192, 193]
Wu-5	Directly binds and inhibits USP10 (reported USP10-targeted compound; IC_{50} ~8.3 μM for USP10 enzymatic activity)	Early pharmacological validation; mechanistic cellular study	FLT3-ITD AML cell lines (MV4-11, Molm13, MV4-11R), Ba/F3-FLT3-ITD cells; small-molecule treatment; *in vitro* and *in vivo* AML models; combination with crenolanib	USP10 inhibition shown by *in vitro* DUB enzymatic assay; reduced thermal stability of USP10 (CETSA); USP10 overexpression rescues FLT3-ITD degradation and cell death	Inhibits USP10 activity leading to proteasome-mediated degradation of FLT3-ITD; induces apoptosis in FLT3-ITD AML cells; enhances crenolanib-induced cell death; inhibits FLT3 and AMPKα signaling pathways	[171]
LY-2	Selective USP10 inhibitor with improved potency	Lead optimization/ preclinical evaluation	Solid tumor models including HCC; small-molecule inhibitor	Demonstrated USP10-dependent YAP and p53 destabilization	Strong anti-tumor activity; induces robust apoptosis; improved potency compared to earlier scaffold compounds	[194]

(*Continued*)

TABLE 4 Continued

Compound/ strategy	Specificity	Evidence level	Model system/ delivery approach	On-target validation	Outcomes	References
GL-320	Selective USP10 inhibitor	Abstract-level preclinical study (early mechanistic validation)	NSCLC cell models including cisplatin-resistant lines; *in vitro* small-molecule treatment; combination with cisplatin; cellular and molecular assay platforms	CETSA confirmed intracellular USP10 engagement; functional DDR modulation consistent with USP10 inhibition	Suppresses proliferation and clonogenic survival; re-sensitizes cisplatin-resistant NSCLC cells; induces DNA damage accumulation (γH2AX, 53BP1, PARP1 foci); activates ATM/ATR signaling and G0/G1 arrest; promotes apoptosis and immunogenic cell death (calreticulin exposure, caspase-8 activation, CD47 downregulation); induces autophagy and ER stress responses	[195]
siRNA-mediated USP10 inhibition (genetic silencing strategy)	USP10 (loss-of-function via RNA interference)	Preclinical mechanistic study	PDAC cell lines; HEK293 mechanistic assays; subcutaneous xenograft mouse model; siRNA-mediated USP10 knockdown	USP10–PLK1 interaction confirmed via Co-IP and pull-down assays; USP10 knockdown increases PLK1 ubiquitination; rescue experiments with USP10 over-expression restore PLK1 stability; enzymatic requirement confirmed via USP10 mutant analysis	siRNA-mediated USP10 inhibition decreases PLK1 stability via increased ubiquitination; suppresses PDAC cell proliferation; enhances sensitivity to gemcitabine; reduces tumor growth in xenograft models	[198]
Self-delivering RNA interference (sdRNA) targeting USP10	USP10-specific gene silencing	Preclinical therapeutic evaluation	Mouse and rabbit corneal wound-healing or fibrosis models; cholesterol-conjugated carrier-free siRNA delivery	Reduction of USP10 mRNA through qPCR	Prevents corneal wound reopening, reduces inflammation and fibrosis, and preserves epithelial integrity	[174, 175, 179]
Peptide-based disruption	USP10-Tau protein-protein interaction interface	Preclinical mechanistic proof-of-concept study	Neuronal cell models; *in vitro* peptide treatment targeting USP10–Tau binding interface; biochemical aggregation assays	Disruption of USP10-Tau interaction confirmed via binding or interaction assays; increased USP10-mediated Tau deubiquitination; decreased Tau aggregation and phosphorylation levels	Peptides that block USP10-Tau interaction reduce Tau deubiquitination, suppress Tau aggregation and hyperphosphorylation induced by USP10 and amyloid-β signaling context	[197]

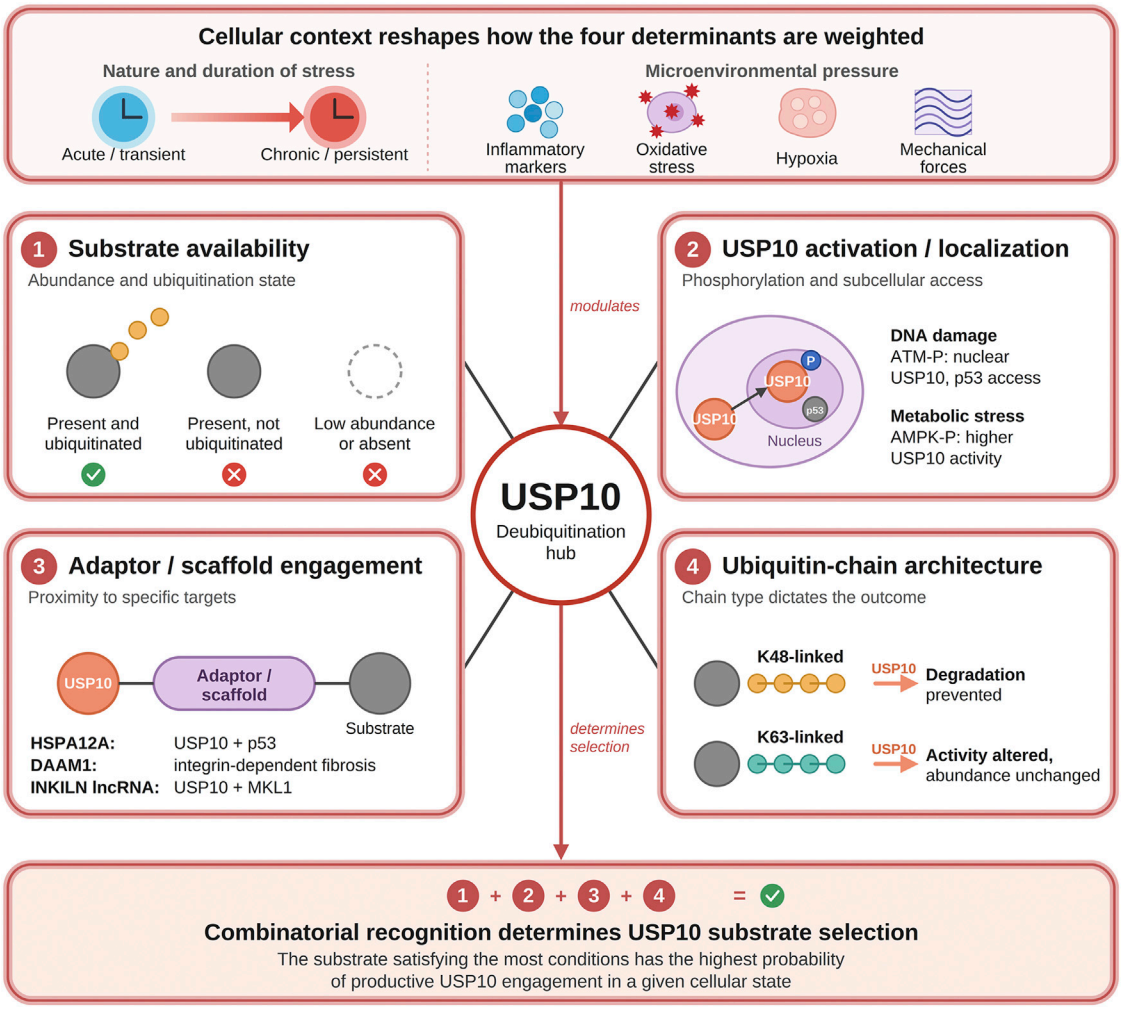


FIGURE 6
Schematic representation of the proposed model for the context-dependent function of USP10. USP10 substrate selection is proposed to depend on the combined influence of four determinants: (1) substrate availability and ubiquitination state, (2) USP10 activation and subcellular localization, (3) adaptor or scaffold engagement, and (4) ubiquitin-chain architecture. DNA damage-associated ATM-dependent phosphorylation may promote nuclear USP10 activity and p53 access, whereas metabolic stress-associated AMPK signaling may enhance USP10 activity. Adaptor proteins and scaffolds, including HSPA12A, DAAM1, and the INKILN lncRNA–MKL1 axis, may facilitate context-specific interactions with target proteins. Ubiquitin-chain topology further influences substrate fate, with K48-linked chains generally associated with proteasomal degradation and K63-linked chains more commonly regulating protein activity or signaling. These determinants are modulated by the nature and duration of stress and the surrounding microenvironment, including inflammation, oxidative stress, hypoxia, and mechanical forces. The framework proposes that combinatorial recognition of these factors determines the likelihood of productive USP10–substrate engagement and the resulting cellular outcome.

increasing its cellular abundance [80]. Thus, substrate selection and ubiquitin-chain context are closely linked determinants of USP10 function.

A second layer of specificity may be provided by protein–protein interactions and molecular scaffolds that regulate USP10 localization, substrate accessibility, and catalytic activity. For example, HSPA12A facilitates the interaction between USP10 and p53 in cardiac fibroblasts [60], illustrating how regulatory partners can influence substrate-specific USP10 functions. Separately, DAAM1 has been identified as a binding partner of USP10 through its FH2 domain and acts as a negative regulator of its deubiquitinase activity. DAAM1 also promotes USP10 association with actin-stress fibers, potentially restricting its activity toward integrin substrates. Consequently, DAAM1 knockdown reduces β1-and β5-integrin ubiquitination, increases their total and cell-surface abundance, and enhances αv-integrin-dependent fibronectin recycling. These findings suggest that protein–protein interactions can regulate USP10 through distinct mechanisms, including substrate recruitment and catalytic inhibition, thereby influencing downstream signaling and fibrotic outcomes in a context-dependent manner [177]. Subcellular localization and post-translational modifications provide additional layers of regulation that influence USP10 activity and substrate specificity. Cellular stress can alter USP10 phosphorylation and intracellular distribution, thereby changing its access to potential substrates. For example, DNA damage induces ATM-dependent phosphorylation of USP10 and promotes its nuclear accumulation, facilitating its interaction with nuclear substrates such as p53. Conversely, AMPK-dependent phosphorylation has been associated with

increased USP10 deubiquitinase activity in the cytoplasm during metabolic stress. Ubiquitination provides an additional regulatory mechanism by influencing substrate stability, activity, and protein interactions. Although K48-linked ubiquitination commonly targets proteins for proteasomal degradation, K63-linked ubiquitination often regulates signaling and intracellular trafficking [200]. For example, AMPKα undergoes predominantly K63-linked ubiquitination in a reported experimental system, which may interfere with its interaction with LKB1 [83]. Under energy stress, USP10-mediated deubiquitination of AMPKα facilitates its interaction with LKB1 and promotes AMPK activation without necessarily altering AMPKα protein abundance. Although ubiquitination can also promote AMPKα degradation under certain conditions [201], these findings illustrate that the functional consequences of ubiquitination depend on the ubiquitin-chain linkage and cellular context. Together, these observations suggest that phosphorylation, subcellular compartmentalization, and ubiquitin-chain architecture can collectively influence USP10 activity, substrate accessibility, and downstream signaling. Identifying the E3 ligases responsible for specific ubiquitin linkages on AMPKα may further clarify how cells regulate USP10-dependent signaling under different physiological conditions. Substrate recognition may also involve regulatory regions and structural features beyond the catalytic pocket. USP10 contains an N-terminal regulatory region in addition to its C-terminal catalytic domain, and its interaction network includes numerous regulatory proteins. These regions may contribute to substrate docking, conformational regulation, autoinhibition, or recruitment into multiprotein complexes [202]. The molecular basis of most individual USP10–substrate interactions remain incompletely characterized. Consequently, reported associations should be distinguished from direct evidence of demonstrated binding. For example, changes in SMAD4 [122] protein levels following USP10 knockdown may indicate a functional relationship but do not, in themselves, establish a direct interaction, which requires supporting experimental evidence. Defining these interactions at structural and biochemical levels will be important for determining whether USP10 possesses shared recognition principles across different substrates or instead relies predominantly on context-specificity.

Evidence-based assessment of USP10 substrates and signaling pathways

Although USP10 has been implicated in diverse biological processes, the strength of mechanistic evidence supporting individual substrate–USP10 relationships vary considerably across studies. To distinguish experimentally established mechanisms from preliminary or associative observations, we classified the reported substrates and pathways according to the type, depth, and consistency of supporting evidence (Supplementary Table S1). Grade A represents strong causal evidence, characterized by direct USP10-mediated deubiquitination, complementary loss- and gain-of-function approaches, *in vivo* validation, and additional causal support through independent replication or substrate-specific epistasis/rescue experiments. Grade B denotes moderate evidence, generally supported by biochemical interaction or substrate stabilization together with *in vivo* validation, but with limitations such as incomplete mechanistic resolution, indirect effects, or a lack of substrate-specific rescue. Grade C indicates limited evidence, including findings primarily derived from cell-based or *ex vivo* systems, studies relying on non-selective pharmacological inhibitors, or proposed substrate relationships for which direct USP10-dependent deubiquitination has not been established. Grade D denotes associative or inferential evidence, such as expression correlations, clinical associations, or pathway-level observations without direct biochemical evidence linking USP10 to the proposed substrate. Together, this framework helps to clarify which USP10 mechanisms are well supported and which require further experimental validation.

Challenges and future perspectives

Despite substantial progress in understanding USP10 biology, significant gaps remain. The precise upstream regulators of USP10, as well as USP10's full interactome across different cell types and tissues, are not fully defined. Leveraging single-cell and spatial transcriptomics will provide high-resolution maps of USP10 expression and activity, revealing context-specific roles in health and disease. Such approaches may uncover previously unrecognized substrates or signaling pathways, enabling the rational design of targeted interventions. Importantly, USP10's role in tissue regeneration and pathology presents opportunities for developing therapies that simultaneously promote protective processes (e.g., regenerative wound healing, autophagy) while inhibiting pathogenic functions (e.g., tumor growth, tauopathy, fibrosis), potentially offering disease-modifying benefits across multiple conditions.

Author contributions

MAS: Formal Analysis, Writing – original draft, Conceptualization, Writing – review and editing, AB: Formal Analysis, Writing – original draft, Conceptualization, Writing – review and editing, AMB: Project administration, Funding acquisition, Writing – review and editing, Supervision, Conceptualization. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was supported by grants from the National Eye Institute, National Institutes of Health (R01 EY024942, R44EY038138), US Department of Veteran's Affairs Biomedical Laboratory Research and Development Service Merit Review Award (I01 BX005360) to AMB, and an unrestricted grant to the Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness.

Acknowledgments

The authors acknowledge the pioneering contributions of researchers in the fields of protein homeostasis, ubiquitin-

proteasome system, and deubiquitinase biology, whose foundational and ongoing work has shaped our current understanding of ubiquitin signaling in physiology and disease. We are grateful to the scientific community for generating high-quality experimental and conceptual advances that informed and inspired this review. The authors sincerely thank Dale Hunter, PhD (Department of Ophthalmology and Visual Sciences) for assistance with proofreading, insightful feedback, and careful factual review of the manuscript. The authors are grateful to Arun Kumar Venkatesan, PhD (Department of Ophthalmology and Visual Sciences) for his insightful comments and input on the mitochondria section of this review. We acknowledge the use of the STRING (version 12.5) online database for protein-protein interaction network analysis. Predicted structure of USP10 obtained from the AlphaFold Protein Structure Database. The figures are created with BioRender.com.

Conflict of interest

AMB declares a conflict of interest due to an affiliation with DUB Therapeutics. Inc.

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.ebm-journal.org/articles/10.3389/ebm.2026.11322/full#supplementary-material

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