

Roles of deubiquitinases in urologic cancers (Review)

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Abstract. Human health is endangered by the occurrence and progression of urological cancers, including renal cell

carcinoma, prostate cancer and bladder cancer, which are usually associated with the activation of oncogenic factors and inhibition of cancer suppressors. The primary mechanism for protein breakdown in cells is the ubiquitin-proteasome system, whilst deubiquitinases contribute to the reversal of this process. However, both are important for protein homeostasis. Deubiquitination may also be involved in the control of the cell cycle, proliferation and apoptosis, and dysregulated deubiquitination is associated with the malignant transformation, invasion and metastasis of urologic malignancies. Therefore, a comprehensive summary of the mechanisms underlying deubiquitination in urological cancers may provide novel strategies and insights for diagnosis and treatment. The present review aimed to methodically clarify the role of deubiquitinating enzymes in urinary system cancers as well as their prospective application prospects for clinical treatment.

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Abbreviations: RCC, renal cell carcinoma; PCa, prostate cancer; BCa, bladder cancer; UPS, ubiquitin-proteasome system; DUBs, deubiquitylating enzymes; Ub, ubiquitin; PIP2, phosphatidylinositol 4,5-diphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PDK1, 3-phosphoinositide-dependent kinase 1; PTEN, phosphatase and tensin homologue; USP, ubiquitin-specific protease; OC, ovarian cancer; CSCC, cervical squamous cell carcinoma; HCC, hepatocellular carcinoma; OSCC, oral squamous cell carcinoma; CRC, colorectal cancer; UCHL5, ubiquitin C-terminal hydrolase L5; ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung cancer; PC, pancreatic carcinoma; NF- κ B, nuclear factor κ B; NLS, nuclear localization sequences; TNF, tumor necrosis factor; TRAF2, TNF receptor-associated factor 2; BCL-3, B-cell lymphoma 3; CYLD, lysine 63 deubiquitinase; IL, interleukin; BC, breast cancer; OS, osteosarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinases; RTK, receptor tyrosine kinase; GC, gastric cancer; CC, colon cancer; TAD, trans-activation domain; MDM2, mouse double minute 2 homolog; TGF- β , transforming growth factor- β ; Smad, SMA and MAD-related protein; FBXW7, F-box and WD repeat domain containing 7; DC, destruction complex; APC, adenomatous polyposis coli; GSK3 β , glycogen synthase kinase-3 β ; CK1 α , casein kinase 1 α ; β -TrCP, β -transducin repeat-containing protein; TLE, transducing-like enhancer protein; TCF, T-cell factor; UCHL3, ubiquitin c-terminal hydrolase-L3; LEF, lymphoid enhancer-binding factor; YAP, yes-associated protein 1; LATS1/2, large tumor suppressor 1/2 kinases; MINDY1, motif interacting with ubiquitin-containing novel DUB family-1; UBD, ub binding domain; AR, androgen receptor; EZH2, enhancer of zeste homolog 2

Key words: RCC, PCa, BCa, deubiquitinase, targeted therapy

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1. Introduction

Urological cancers encompass malignancies that arise in the organs associated with the urinary system, predominantly comprising renal cell carcinoma (RCC), prostate cancer (PCa) and bladder cancer (BCa). According to global cancer statistics for 2020, there were ~2.4 million novel instances of urinary system neoplasms, constituting 12.5% of all malignancies worldwide (1). The risk factors associated with PCa primarily include familial predisposition, racial background, advanced age, obesity and several environmental and genetic influences. Adenocarcinomas can be categorized into androgen-sensitive and androgen-insensitive subtypes. Treatment modalities for PCa include active surveillance, chemotherapy, radiotherapy, hormone therapy, surgical intervention and cryotherapy (2). Sex, obesity, hypertension, smoking and chronic kidney disease are risk factors for RCC. Whilst it is possible to treat RCC surgically, local recurrence occurs in 2-5% of patients and in 20-30% of patients with distant metastases. Postoperative

adjuvant therapy includes hormone therapy, radiotherapy, immunotherapy, vaccines and targeted drugs. These therapies, however, have not yielded any evidence of improved patient survival (3). Risk factors for BCa include smoking, parasitic infections, chronic inflammation, sex, age, occupational exposure and genetic factors. Depending on whether a tumor has invaded the bladder muscular layer, it can be classified as non-muscle-invasive BCa or muscle-invasive BCa. The treatment of BCa includes surgical resection, immunotherapy, chemotherapy, radiotherapy and antibody-drug conjugates (4). An increasing amount of data indicate that investigating novel therapeutic approaches for advanced urologic malignancies requires a thorough understanding of the molecular pathways underlying urologic neoplasia (5,6).

An important post-translational modification is ubiquitination. The complex signaling network created by intricate interactions between the ubiquitin-proteasome system (UPS) and its substrates are necessary for regulating a number of bodily physiological processes, including signal transmission, cellular metabolism, immunological stress responses and cell cycle progression (7). In eukaryotes, the UPS is responsible for >80% of protein turnover. The main components of the ubiquitination process are deubiquitylating enzymes (DUBs), ubiquitin (Ub), ubiquitin-activating enzyme E1, ubiquitin-conjugating enzyme E2, ubiquitin ligase enzyme E3 and 26S proteasome (8). First, to create an E1-Ub complex, unbound Ub molecules are activated by E1 in an ATP-dependent manner and connected by thioester linkages. Next, the activated Ub is transferred to the E2 active site cysteine residue. Finally, the interaction between the E2-Ub complex and E3 facilitates the transfer of activated Ub to the lysine residue of the substrate protein (9). A total of seven lysine residues (K6, K11, K27, K29, K33, K48 and K63) are notable features of ubiquitin. These residues are ubiquitinated to produce different polyubiquitin chains (10). Target substrates are typically delivered to the proteasome for destruction by polymerized ubiquitinated chains of K11, K29 and K48. Despite this, K63, K6, K27, K33 and other polymerized ubiquitinated chains, are involved in many critical cellular processes, including transcriptional control, DNA repair and signal transduction, whilst protecting their target substrates from damage (Fig. 1) (11).

2. DUBs in signaling pathways associated with urological tumors

Abnormal regulation of DUBs has been extensively studied and reported to be closely associated with the occurrence and progression of human tumors, including malignant tumors of the urinary system (12). It has been reported that a large number of DUBs can act as both oncogenic factors and tumor suppressors (12). Therefore, an exhaustive overview of these DUBs may lead to innovative approaches for the treatment of urinary system tumors. The present review provides an extensive synopsis of the most recent developments in DUBs within urological malignancies, encompassing their classification, structure and function. Furthermore, it highlights the crucial regulatory mechanisms through which DUBs modulate signaling pathways relevant to urological tumors (Table I).

PI3K/AKT pathway. A key element of the PI3K/AKT pathway is transmission of signals within cells, and its aberrant activation can lead to rapid growth, reproduction and abnormal regulation of angiogenesis in cancer cells (13). PI3K is an isodimer composed of the regulatory subgroup p85 and catalytic subgroup p110, so it can be categorized into PI3KI, PI3KII and PI3KIII types based on their structure. PI3K is not primarily in a specific organelle, but acts as an intracellular phosphatidylinositol kinase on the plasma membrane of the cell (14). Transmembrane tyrosine kinase growth factor receptors can activate PI3K, such as EGFR and insulin-like growth factor receptor 1. Phosphorylation of phosphatidylinositol 4,5-diphosphate (PIP2) activated by PI3K is then converted to phosphatidylinositol 3,4,5-triphosphate (PIP3) (15). Subsequently, 3-phosphoinositide-dependent kinase 1 (PDK1) and AKT are recruited to the plasma membrane, where PDK1 phosphorylates threonine at position 308 of AKT, resulting in AKT activation (16). Once activated, AKT phosphorylates its downstream targets, including mTOR. Therefore, it is a major factor in the development and metastasis of cancer (17,18).

Of note, phosphatase and tensin homologue deleted on chromosome 10 (PTEN) could inhibit the activation of the PI3K-PKB signaling pathway by dephosphorylating PIP3 and converting it to PIP2. When *PTEN* is mutated or absent, PIP3 accumulates in cells and uncontrollably activates its downstream signaling (19,20). Both deregulated ubiquitination and deubiquitination can lead to detrimental impacts on PTEN levels and subcellular partitioning, promoting tumorigenesis (21). Furthermore, a diverse range of DUBs, including ubiquitin-specific protease (USP)7 and USP13, have been reported to mediate the deubiquitination of PTEN, thereby disrupting the function of PTEN to promote the PI3K/AKT signaling pathway (21), and the dysregulation of PTEN deubiquitination could lead to the tumorigenesis of PCa (Fig. 2).

USP7. USP7, also known as herpes virus-associated protease, is a DUB enzyme belonging to the USPs family. It is a cysteine peptidase that comprises five distinct domains (22). USP7 is mostly found in the nucleus and is essential for controlling the stability of several proteins involved in several cellular activities, including immunological response, infection by viruses, DNA damage reaction, transcriptional regulation and epigenetic control of gene overexpression (23). Mechanistically, USP7 may interact with K13 and K289 to deubiquitinate PTEN *in vivo* and *in vitro*, reducing its single-stranded structure and leading to nuclear rejection and PTEN inactivation, thereby promoting cancer occurrence and metastasis. Song *et al* (24) reported that USP7-mediated deubiquitination of PTEN could lead to a reduction in its inhibitory effect on PCa cell proliferation.

USP13. Formerly known as isopeptidase T, USP13 is a member of the USPs family of enzymes and is categorized as a deubiquitinating enzyme. Its roles include controlling the course of the cell period, repairing damage to DNA systems, myoblast development, endoplasmic reticulum quality control mechanisms and autophagy. Many malignant tumors, including ovarian cancer (OC), cervical carcinoma (CC) and hepatocellular carcinoma (HCC), have elevated USP13 expression. Enhanced USP13 activity promotes tumor cell proliferation by upregulating a range of carcinogenic factors such as myeloid cell leukemia-1 and c-MYC. However, in certain malignancies

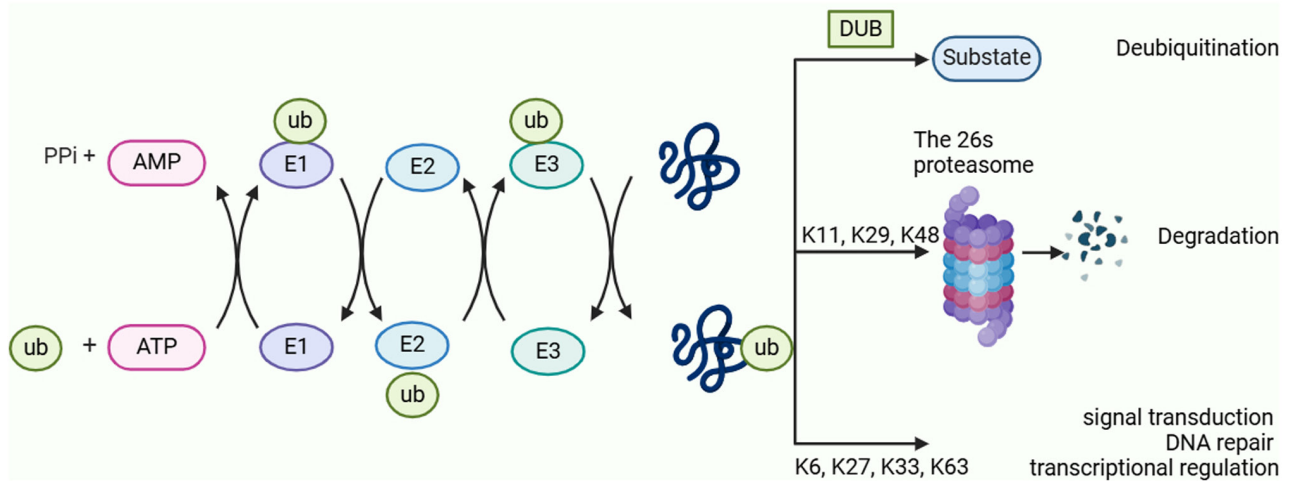


Figure 1. Ubiquitination processes. Ubiquitination is a crucial protein modification process that involves ubiquitin, E1, E2, E3 ligases, DUBs and the 26S proteasome. Firstly, free ubiquitin molecules are activated by ATP-dependent E1 and linked to form an E1-Ub complex. Upon reaching the cysteine residue of the active site of E2, the activated Ub then interacts with E3 to transfer onto the lysine residues of substrate proteins. Notably, ubiquitin contains seven lysine residues that can undergo distinct polyubiquitination chains; K11, K29 and K48 chains deliver target substrates for degradation whilst other chains protect targets from degradation and participate in biological processes like signal transduction. The reverse process of ubiquitination is called deubiquitination. Under the catalysis of DUBs, the ubiquitin molecules on the substrates are removed, thus inhibiting the proteasome-mediated degradation. Deubiquitinases are a broad class of proteases with ~100 members that are divided into seven different subfamilies according to structural features. The subfamilies in question comprise the following: USPs, UCHs, OTUs, proteases that are involved in the Machado-Joseph disease domain, metalloenzymes that contain JAMMs domain, a novel DUB family that interacts with Ub (MINDYs), and zinc-finger and UFSP domain protein. Apart from JAMMs, which functions as a metalloprotease subfamily, the remaining six deubiquitinating enzyme families belong to cysteine peptidases. Furthermore, the USP family is composed of >50 members with conserved domains and catalytic sites including the fingers, palm and thumb. A total of four UCH deubiquitinating enzymes, including UCHL1, UCHL3, UCHL5/UCH37 and BRCA1-associated protein 1 exhibit a conserved catalytic domain and high similarity sequence. In humans, the OTU deubiquitinases subfamily consists of sixteen members, and almost every OTU possesses a ubiquitin interaction domain, such as a ubiquitin interacting motif domain, ubiquitin associated domain, or zinc finger domain, in addition to its OTU catalytic domain. Ub, ubiquitin; DUBs, deubiquitylating enzymes; USP, ubiquitin-specific protease; UCH, ubiquitin C-terminal hydrolase; OTU, ovarian tumor proteases; JAMM, Jad1/Pad/Mpn; MINDY, motif interacting with ubiquitin-containing novel DUB family.

such as breast cancer (BC) and colorectal cancer (CRC), the overexpression of USP13 exhibits a tumor-suppressive effect through the upregulation of PTEN (25,26). Recently, Cui *et al* (27) reported that USP13 was involved in PCa by upregulating the PI3K/AKT pathway. Although USP13 can promote PI3K-AKT-induced invasion and metastasis of PCa (27), the underlying mechanism requires further exploration.

USP39. The DUBs family of enzymes includes USP39, which has a central zinc finger ubiquitin-binding domain and a ubiquitin C-terminal hydrolase domain (28). It is involved in the regulation of several biological processes such as cell proliferation, cell cycle progression, apoptosis and pre-messenger RNA splicing (29). Upregulation of USP39 has also been implicated in the pathogenesis of HCC, medullary thyroid carcinoma, oral squamous cell carcinoma (OSCC) and CRC (30-33). Xu *et al* (34) first determined that the knockdown of USP39 significantly impedes the phosphorylation of AKT at Ser473, therefore blocking the activity of the AKT signaling pathway in RCC. However, more investigation is needed to clarify the precise processes behind the function of USP39 in regulating AKT signaling.

Ubiquitin C-terminal hydrolase L5 (UCHL5). UCHL5, also known as ubiquitin carboxy-terminal hydrolase 37, is an important factor regulating deubiquitination and has been reported to be abnormally high expressed in numerous cancers, including CSCC, esophageal squamous cell carcinoma (ESCC), epithelial OC, non-small cell lung cancer (NSCLC) and pancreatic carcinoma (PC) (35-39). Recently,

Cao *et al* (40) reported that overexpression of UCHL5 could activate the AKT/mTOR pathway and further activate the downstream target c-MYC, thus promoting the proliferation and migration of BCa. It remains unknown, therefore, how UCHL5 controls the AKT signaling pathway.

NF- κ B pathway. The protein complex known as nuclear factor κ B (NF- κ B) is an essential nuclear transcription factor in cells and is associated with cancer, inflammatory and autoimmune diseases, viral infections and abnormal development of the immune system (41). It represents an important family of structurally similar transcription factors (Rel proteins), consisting of five members: NF- κ B1 (p50), NF- κ B2 (p52), RelA (p65), RelB and c-Rel (42). The signal transduction pathway of NF- κ B activation primarily comprises two distinct modes: Canonical and non-canonical (43). The NF- κ B protein typically forms homologous or heterodimers with p65 and p50 or is rendered inactive in the cytoplasm by binding to the suppressor I κ B, thus causing a trimeric complex to form. Upon binding of the upstream signaling factor tumor necrosis factor (TNF) to the cell membrane surface receptor, conformational changes occur within the receptor, transmitting the signal to IKK kinase (I κ B kinase), causing the IKK complex made up of IKK- α , IKK- β and IKK- γ to become activated. This IKK complex then phosphorylates the I κ B protein, causing it to separate from the trimeric complex. Subsequently, nuclear localization sequences (NLS) are exposed on the NF- κ B dimer, allowing for rapid translocation from the cytoplasm into the nucleus for the activation of target genes (44).

Table I. Urologic cancer-associated deubiquitylating enzymes.

A, PI3K/AKT signaling pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Song <i>et al.</i> , 2008	USPs	USP7	PCa	PTEN	Suppression of PTEN	Oncogenic factors	(24)
Cui <i>et al.</i> , 2022		USP13	PCa	Not reported	Activates PI3K/AKT pathway	Oncogenic factors	(27)
Xu <i>et al.</i> , 2018		USP39	RCC	AKT	Activates PI3K/AKT pathway	Oncogenic factors	(34)
Cao <i>et al.</i> , 2022	UCHs	UCHL5	BCa	AKT	Activates PI3K/AKT pathway	Oncogenic factors	(40)
B, NF-κB pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Sim <i>et al.</i> , 2018; Yuan <i>et al.</i> , 2023	USPs	CYLD	RCC/BCa	IKKβ/IκB	Suppression of NF-κB pathway	Tumor suppressor	(54,55)
Man <i>et al.</i> , 2019 and Man <i>et al.</i> , 2021		USP13	BCa	Not reported	Suppression of NF-κB pathway	Tumor suppressor	(56,57)
Baohai <i>et al.</i> , 2019		USP17	PCa	Not reported	Suppression of NF-κB pathway	Tumor suppressor	(61)
C, RAS/RAF/MEK/ERK pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Zhang <i>et al.</i> , 2019	USPs	USP9X	PCa	ERK	Suppression of MAPK pathway	Tumor suppressor	(68)
Hu <i>et al.</i> , 2020		USP19	RCC	ERK	Suppression of MAPK pathway	Tumor suppressor	(69)
Xu <i>et al.</i> , 2018		USP39	RCC	ERK	Activates MAPK pathway	Oncogenic factors	(34)
D, p53 pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Stevenson <i>et al.</i> , 2007	USPs	USP2a	BCa/PCa	MDM2	Stabilize MDM2	Oncogenic factors	(94)
Sun <i>et al.</i> , 2010		USP7	PCa	MDM2	Stabilize MDM2	Oncogenic factors	(97)
Devrim <i>et al.</i> , 2020; Fong <i>et al.</i> , 2016		USP28	BCa	p53	Activates p53 pathway	Oncogenic factors	(102,103)
E, TGF-β pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Wosnitzer <i>et al.</i> , 2014; Dirac <i>et al.</i> , 2010	USPs	USP26	PCa	AR	Suppression of TGF-β pathway	Tumor suppressor	(114,115)

Table I. Continued.

F, MYC pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Ge <i>et al</i> , 2021	USPs	USP16	PCa	c-MYC	Stabilize c-MYC	Oncogenic factors	(131)
Li <i>et al</i> , 2024		USP43	BCa	c-MYC	Stabilize c-MYC	Oncogenic factors	(138)
G, Wnt/ β -catenin pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Liu <i>et al</i> , 2023	UCHs	UCHL3	BCa	CTNNB1	Stabilize CTNNB1	Oncogenic factors	(150)
Cheng <i>et al</i> , 2019	USPs	USP25	PCa	TNKS	Stabilize TNKS	Oncogenic factors	(156)
Zhao <i>et al</i> , 2020		USP34	RCC	Not reported	Activates Wnt pathway	Oncogenic factors	(161)
H, Hippo pathway							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Gu <i>et al</i> , 2024	USPs	CYLD	PCa	YAP	Suppression of YAP	Tumor suppressor	(167)
Luo <i>et al</i> , 2021	MINDY	MINDY1	BCa	YAP	Stabilize YAP	Oncogenic factors	(172)
I, Other DUBs							
First author/s, year	Types	DUBs	Urologic cancers	Substrates in urologic cancers	Deubiquitination-induced change	Potential role in urologic cancers	(Refs.)
Ye <i>et al</i> , 2022	USPs	USP10	PCa	H2A	Stabilize H2A	Oncogenic factors	(177)
Chen <i>et al</i> , 2017		USP21	BCa	EZH2	Stabilize EZH2	Oncogenic factors	(182)
Lv <i>et al</i> , 2011; Guo <i>et al</i> , 2022; Nag <i>et al</i> , 2020		USP22	PCa/BCa	MYC	Not reported	Oncogenic factors	(188-190)

USP, ubiquitin-specific protease; DUBs, deubiquitylating enzymes; CYLD, lysine 63 deubiquitinase; UCHL5, ubiquitin C-terminal hydrolase L5; UCHL3, ubiquitin C-terminal hydrolase L3; MINDY1, motif interacting with ubiquitin-containing novel DUB family-1; PCa, prostate cancer; RCC, renal cell carcinoma; BCa, bladder cancer; PTEN, phosphatase and tensin homologue; ERK, extracellular signal-regulated kinase; MDM2, mouse double minute 2 homolog; AR, androgen receptor; TNKS, tankyase; YAP, yes-associated protein 1; EZH2, enhancer of zeste homolog 2; NF- κ B, nuclear factor κ B; MAPK, mitogen-activated protein kinases; TGF- β , transforming growth factor- β .

TNF receptor-associated factor (TRAF)2, a bifunctional protein that acts as an adaptor and ubiquitin E3 ligase, is one of the major mediators of the TNF receptor. It possesses a carboxy-terminal TRAF domain that can be further divided into two subdomains known as TRAF-N and TRAF-C domains (45). TRAF2 protein induces the activation of I κ B kinase (IKK α and IKK β), leading to the phosphorylation of I κ B α . Additionally, it promotes nuclear translocation and phosphorylation of p65/RelA to promote the downstream signaling cascade of the NF- κ B pathway (46).

An unusual member of the I κ B inhibitor family is B-cell lymphoma 3 (BCL-3) (47). The full-length BCL-3 protein,

with a molecular weight of ~47 kDa, contains the proline-rich N-terminal domain, seven central tandem repeat cdc10 domains (the ankyrin repeat domain) and a serine and proline-rich transcription activation domain at the C-terminal (48,49). Transcriptional regulation in the nucleus is mediated by BCL-3 through its interaction with homodimers of p50 (NF- κ B1) or p52 (NF- κ B2; Fig. 2) (50).

Lysine 63 deubiquitinase (CYLD). As a negative regulator of the NF- κ B pathway, the CYLD protein belongs to the USPs and consists of three glycine-rich cytoskeletal associated protein domains, two proline-rich motifs, a phosphorylation region and the USP catalytic domain (51). Emerging evidence

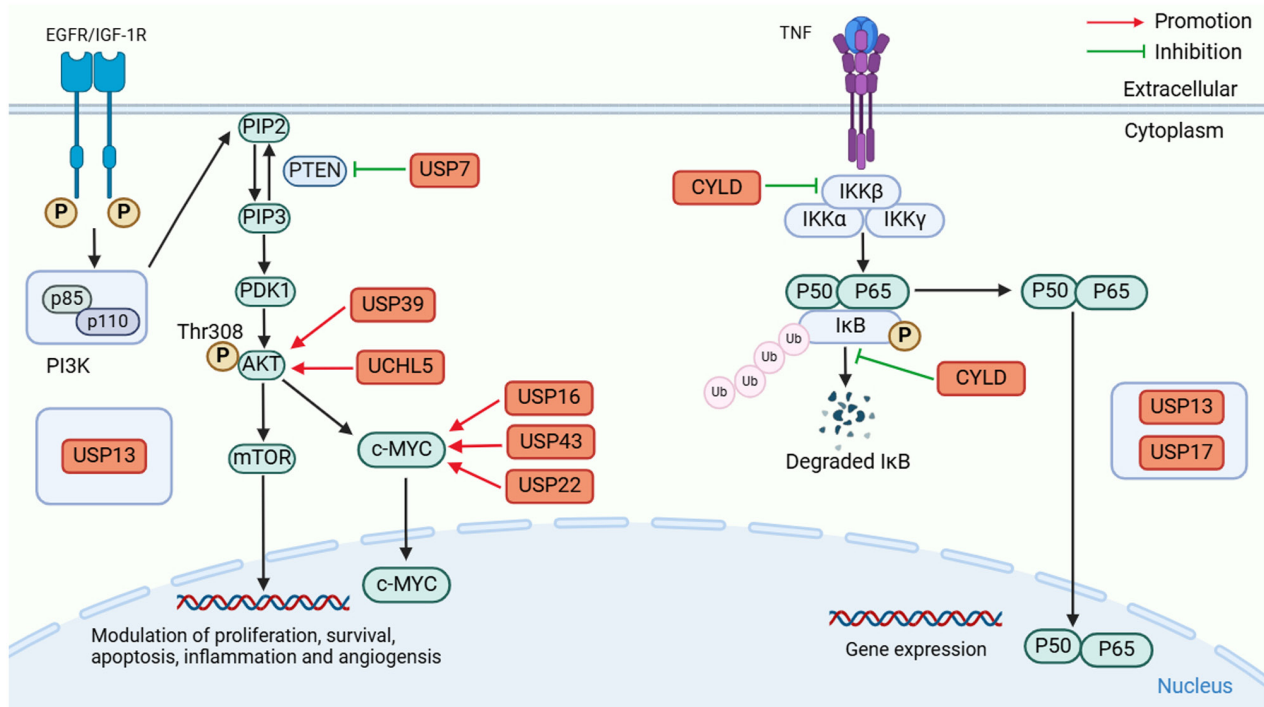


Figure 2. Role of DUBs in the PI3K/AKT, NF- κ B and MYC pathways in urologic cancers. PI3K/AKT pathway: Transmembrane tyrosine kinase growth factor receptors such as EGFR and IGF-1R can activate PI3K. This leads to phosphorylation of PIP2 into PIP3. PDK1 and AKT proteins are then recruited to the plasma membrane, where PDK1 phosphorylates threonine at position 308 of AKT, activating AKT. Once activated, AKT phosphorylates downstream targets, such as mTOR, which serve a crucial role in cancer occurrence and development. Mechanistically, USP7 interacts with K13 and K289 to deubiquitinate PTEN. This reduces its single-stranded form, leading to nuclear rejection and PTEN inactivation, which promotes cancer occurrence and metastasis. Although USP13 could promote PI3K-AKT-induced invasion and metastasis of PCa, further exploration is needed to understand the underlying mechanisms. USP39 knockdown has been reported to markedly inhibit the phosphorylation of AKT at Serine 473, thus preventing the activation of the AKT signaling pathway in RCC. Overexpression of UCHL5 activates the AKT/mTOR signaling pathway, which further activates the downstream target c-MYC, promoting the proliferation and migration of BCa. NF- κ B pathway: The cell membrane receptor undergoes conformational changes when TNF binds to it and transmits a signal to IKK kinase. This leads to the phosphorylation of the I κ B protein and its dissociation from the trimeric complex. Subsequently, nuclear localization sequences are exposed on the NF- κ B dimer, allowing rapid translocation into the nucleus and activation of target genes. The CYLD protein functions by inhibiting the ubiquitination of I κ B and retaining the NF- κ B heterodimer p65/p50 in the cytoplasm, thereby suppressing the proliferation, migration and invasion of BCa cells. Further research is necessary to ascertain how USP13 regulates the NF- κ B signaling pathway and how USP17 regulates these genes or the site it uses to regulate this pathway. MYC pathway: Multiple upstream signaling pathways, including the PI3K/AKT/mTOR pathway, phosphorylate MYC to enhance its DNA-binding ability. Phosphorylated MYC forms a dimer with Max and initiates downstream DNA transcription for cellular growth and proliferation. USP16 knockdown markedly inhibits PCa cell growth. USP43 deubiquitinase activity mostly deubiquitinates c-MYC at K148 and K289, stabilizing it and promoting BCa metastasis. Overexpression of USP43 protein in BCa hinders FBXW7 accessibility and raises the possibility of contact with c-MYC, which prevents c-MYC breakdown. USP, ubiquitin-specific protease; NF- κ B, nuclear factor κ B; EGFR, epidermal growth factor receptor; IGF-1R, insulin-like growth factor-1 receptor; PIP2, phosphatidylinositol 4,5-diphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; CYLD, lysine 63 deubiquitinase; PDK1, phosphoinositide-dependent kinase 1; PTEN, phosphatase and tensin homologue; FBXW7, F-box and WD repeat domain containing 7.

suggests that CYLD is associated with the pathogenesis of several diseases, including cancer, infection, pulmonary fibrosis, neurodegeneration and cardiovascular dysfunction (52). The fundamental process involves CYLD mediating TRAF2 or BCL-3 deubiquitination, which disrupts NF- κ B signaling (53). Sim *et al* (54) reported that CYLD can inhibit IKK β , stabilize I κ B α and retain the NF- κ B heterodimer in the cytoplasm, leading to the blocking of p65/p50 nuclear translocation, hence preventing RCC cells from proliferating. Notably, Yuan *et al* (55) reported that the CYLD protein functions by inhibiting the ubiquitination of I κ B and retaining the NF- κ B heterodimer p65/p50 in the cytoplasm, thereby suppressing the proliferation, migration and invasion of BCa cells.

USP13. USP13 may function as a putative oncogenic protein in PCa by activating the PI3K/AKT signaling pathway (27). Notably, Man *et al* (56,57) reported that USP13 deubiquitinates and stabilizes PTEN protein, and PTEN protein

suppresses NF- κ B activation by inhibiting the PI3K/AKT pathway, thereby preventing the nuclear translocation and DNA-binding ability of NF- κ B subunits. In conclusion, low USP13 expression can promote the occurrence and progression of BCa. Nevertheless, the chemical control technique of USP13 over the NF- κ B signaling pathway remains poorly understood, and further research is needed.

USP17. USP17, known as DUB3, comprises a catalytic USP domain, along with two hyaluronic acid (and RNA) binding motifs (58), which is controlled by interleukin (IL)-4 and IL-6 cytokines. The formation of T helper cell 17 cells, inflammation, cell motility and carcinogenesis are all associated with the abnormal expression of USP17 (59). Research has demonstrated an association between the expression and function of USP17 and several cancer types, including OSCC, NSCLC, BC, CRC, CSCC and osteosarcoma (OS) (58). USP13 and USP17, as deubiquitinating enzymes, are not localized in a specific organelle, but widely distributed in the cytoplasm and

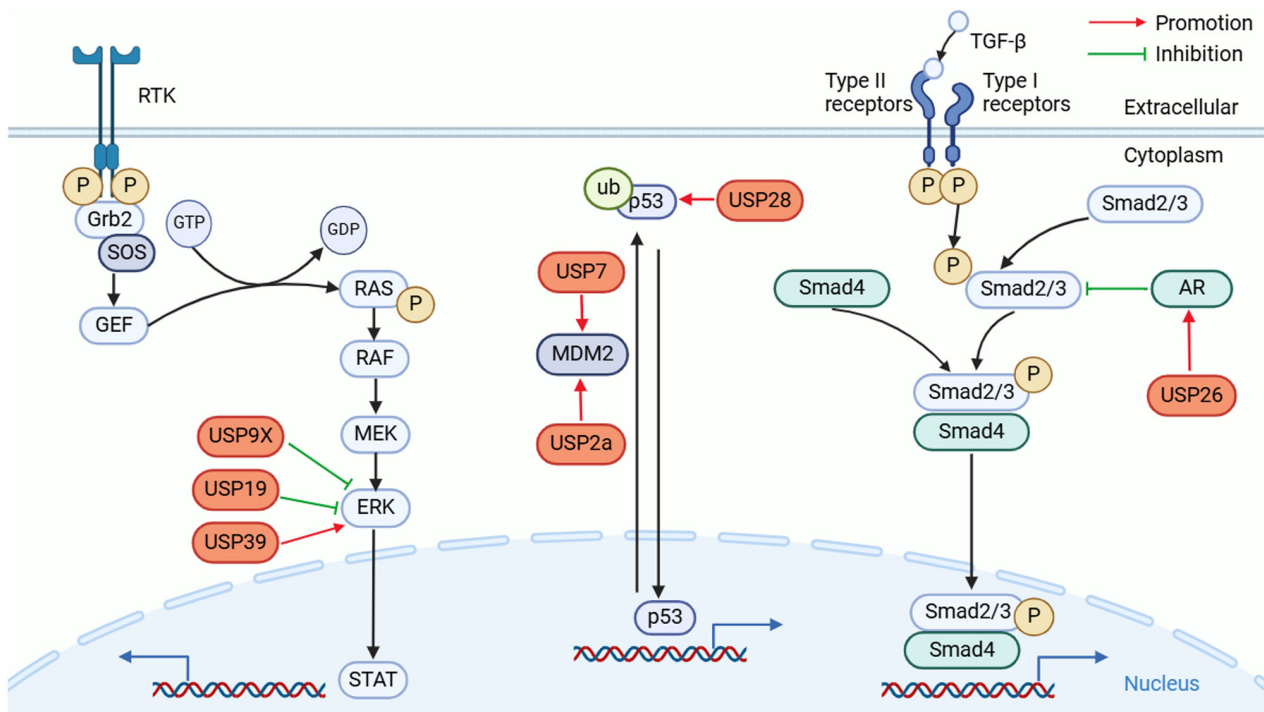


Figure 3. Role of DUBs in the RAS/RAF/MEK/ERK, p53 and TGF- β pathways in urologic cancers. RAS/RAF/MEK/ERK pathway: RAS proteins with GTPase activity are activated by upstream RTKS, and activated RAS activates RAF. Activated RAF further activates MEK, which in turn activates ERK, the sole downstream substrate. Finally, the activated ERK enters the nucleus and initiates a series of physiological and biochemical reactions. USP9X knockdown upregulates the ERK signaling pathway, thereby further promoting cancer cell invasion. These findings validate the effectiveness of USP9X as a tumor suppressor; however, the substrates of USP9X require further investigation. The overexpression of USP19 notably decreases ERK levels, whereas USP19 knockdown increases ERK phosphorylation, thereby promoting RCC cell proliferation. However, the underlying mechanisms remain unclear. Downregulation of USP39 markedly inhibits the phosphorylation of ERK at the Thr202/Tyr204 site, thereby preventing activation of the MAPK pathway. p53 pathway: When cells suffer DNA damage, p53 is activated, further preventing cell proliferation and initiating apoptosis. By deubiquitinating MDM2, USP2a critically controls the p53 pathway, thereby elevating the intracellular levels of MDM2 and subsequently downregulating p53. Similarly, USP7 enhances the stability and activation of p53 through the deubiquitination of MDM2. Mechanistically, USP28 deubiquitinates and stabilizes p53 in BCa cells. However, due to the limited association studies on p53 and USP28, the underlying mechanisms remain to be further explored. TGF- β pathway: Upon conjugation with a TGF- β activator, activated TGF- β binds to TGF- β RII and TGF- β RI to phosphorylate transcription factors by forming a tetrameric complex. Smads 3 and 2, Smad complex DNA-binding cofactors, regulate gene expression by recruiting transcription factors. USP, ubiquitin-specific protease; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinases; Grb2, growth factor receptor-bound protein 2; GEF, guanine exchange factor; GTP, guanosine triphosphate; GDP, guanosine diphosphate; MDM2, mouse double minute 2 homolog; TGF- β , transforming growth factor- β ; SMAD, SMA and MAD-related protein; AR, androgen receptor.

nucleus. Under different conditions, the localization of USP13 and USP17 in the cell may change (60). Baohai *et al* (61) reported that the inhibition of USP17 hinders NF- κ B signaling through the facilitation of reactive oxygen species generation to inhibit the progression of PCa. However, more research is needed to elucidate how USP17 controls these genes or how it regulates the NF- κ B signaling pathway.

RAS/rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase (MAPK) kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway. The MAPK signaling pathway, a crucial component of the eukaryotic signal transduction network, functions as a major signaling cascade that regulates the processes of apoptosis (programmed cell death), cell division, proliferation, and the cellular reaction of irritability in both healthy and pathological settings. MAPK is a family of serine-threonine kinases that has undergone evolutionary conservation. It is composed of four separate subfamilies: ERK, p38, JNK and BMK1 (sometimes referred to as ERK5), which correspond to four conventional MAPK pathways (62). The most notable signaling cycle among all

MAPK signaling pathways is the RAS/RAF/MEK/ERK pathway (63). Binding of growth-promoting elements to their receptors triggers activation of receptor tyrosine kinase (RTK). This, in turn, leads to the recruitment of the growth factor receptor bound protein 2 and subsequently activates guanine nucleotide exchange factors. The signal is then transmitted to the RAS, which directly interacts with the RAF to form a transient membrane-anchored signal (64). Activated RAF triggers the MEK by making a serine site in its catalytic loop phosphorylated and ERK is subsequently activated by MEK. This then phosphorylates several substrates connected to the cytoplasm and the membrane of the cell (65). Cancer mutations with the highest prevalence are driver mutations in RAS, primarily KRAS, which occurs in ~30% of all types of cancer and affects ~10% of all patients with cancer (66,67). Targeting this route has been reported in multiple studies to have a major impact on the growth and progression of urinary system cancers by involving multiple DUBs (34,68,69) (Fig. 3).

USP9X. On chromosome Xp11.4, USP9X is a highly conserved DUB that is a member of the USP group (70). The expression level of USP9X is widely associated with cell

cycle regulation, signaling pathway conduction, ribosomal stalling and tumorigenesis. Prior research has demonstrated the marked impact USP9X serves in many malignancies, including laryngeal carcinoma, BC, glioblastoma and lung cancer (71-73). Zhang *et al* (68) reported that USP9X may act as a tumor suppressor in PCa. Compared with healthy tissues, USP9X expression was downregulated in PCa tissues, and ERK was notably increased. Furthermore, *USP9X* depletion upregulated ERK signaling, resulting in an increase in matrix metalloproteinase 9 protein levels and dynamin-related protein 1 phosphorylation, thereby further promoting cancer cell invasion. These results indicate that USP9X is an efficient tumor suppressor; nevertheless, more investigation is needed to identify USP9X substrates.

USP19. USP19 is a DUB that is essential for lipogenesis, cellular metabolism and immunological responses (74,75). Furthermore, prior research has indicated that USP19 is implicated in a number of malignancies, such as stomach cancer (GC), CRC and HCC (74,76,77). Hu *et al* (69) analyzed The Cancer Genome Atlas and Gene Expression Omnibus databases and reported that USP19 expression was downregulated in RCC and that USP19 knockdown led to tumor progression and poor prognosis. Notably, the study reported that USP19 knockdown enhanced ERK phosphorylation, and USP19 overexpression markedly reduced ERK levels, which in turn promoted clear cell RCC proliferation both *in vitro* and *in vivo*. These findings suggest that USP19 expression is linked to ERK pathway activity and may have tumor-suppressive properties. Nevertheless, more research is required to elucidate the underlying mechanisms.

USP39. USP39 is a member of the USP family of DUBs, with a central zinc finger ubiquitin-binding domain and a ubiquitin C-terminal hydrolase domain (78). USP39 is involved in multiple cellular processes, including spliceosome formation, spindle stabilization and the cell cycle (79). Many studies have reported that USP39 is overexpressed in HCC, BC, colon cancer (CC) and RCC (78,80,81). Xu *et al* (34) reported that USP39 promotes the MAPK signaling and exerts an oncogenic effect in RCC. Small interfering RNA was used to reduce USP39 expression in RCC cells, and the study reported that this markedly reduced the ability of the cells to proliferate and spread. Mechanistically, the deletion of *USP39* led to a notable reduction in the expression levels of apoptotic proteins and G2/M phase-associated proteins. Furthermore, phosphorylation of ERK at the Thr202/Tyr204 region was dramatically suppressed by downregulating USP39, which prevented the MAPK pathway from being activated. The aforementioned findings suggest that USP39 is a potential target for RCC therapy.

p53 pathway. The TP53 gene, commonly referred to as p53, encodes the tumor protein, which is a known tumor suppressor in humans and has been identified as the most strongly associated with human tumorigenesis to date. It is also associated with ~50% of all human tumors (82). Human p53 is a 4x393 amino acid homotetramer consisting of an intrinsically disordered N-terminal trans-activation domain (TAD), proline (Pro)-rich region, structured DNA-binding domain, tetramerization domain linked by an elastic linker, and intrinsically disordered C-terminal

regulatory domain (83). Cell cycle arrest, DNA repair, metabolic changes, antioxidant and anti-angiogenic effects, autophagy, senescence and apoptosis are just a few of the reactions that p53 orchestrates. It can activate multiple transcriptional targets in response to cellular stress or DNA damage (84).

Mouse double minute 2 homolog (MDM2) is an E3 ligase composed of a p53-binding domain at the N-terminus, a central region containing a NLS, a nuclear export signal and a RING finger domain at the C-terminus (85). MDM2 negatively regulates p53 by binding to its transcriptional activation domain to prevent the interaction of transcription elements, mediating p53 covalent binding to ubiquitin proteins to be degraded by proteolytic enzymes, and expulsion from the nucleus (86,87). A comprehensive overview of several DUBs that control p53 signaling may offer novel insights into the occurrence and progression of tumors of the urinary system (Fig. 3).

USP2a. The enzyme known as USP2a deubiquitinates cysteine proteases. USP2a regulates the function of multiple important cell growth regulators and signal transduction factors. USP2a serves a role in carcinogenesis, stimulation of NF- κ B and interferon modulation (88,89). USP2a is upregulated in several cancers, including BC, HCC and OC (90-92). Kim *et al* (93) assessed the function of USP2a in BCa cells and reported that USP2a stabilizes and deubiquitinates MDM2, which is a specific target of USP2a. The study also reported that silencing USP2a notably decreased MDM2 protein levels and cell proliferation capacity, implying that USP2a is an MDM2-associated positive regulator. In addition, it was also reported that during the development of PCa, USP2a was overexpressed, leading to the inhibition of p53 by stabilizing MDM2. Therefore, the inhibition of USP2a activity may provide a novel strategy for cancer treatment (94).

USP7. USP7 may activate the PI3K/AKT signaling pathway. USP7 participates in the regulation of multiple cellular pathways and its expression is often dysregulated in human malignancies (22). Studies have reported that USP7 expression is upregulated in PCa and strongly associated with tumor progression (95,96). Mechanistically, USP7 stabilizes MDM2 through its specific deubiquitinase activity, which increases the intracellular level of MDM2 and downregulates p53, leading to the promotion of tumor development. Consequently, the creation of USP7 inhibitors is a successful patient therapy strategy (97).

USP28. A member of the USPs family, USP28 possesses both a USP domain and a C-terminal extension domain, is located on chromosome 11q23 (98). In addition, studies have reported an association between USP28 and certain malignancies, such as PC, CRC and GC (99-101). USP28 was reported to be overexpressed in BCa and associated with tumor invasion and growth. Immunohistochemistry and reverse transcription-quantitative PCR revealed that USP28 and p53 were overexpressed in BCa cells, and there was a marked association between them (102). Mechanistically, USP28 deubiquitinates and stabilizes p53 in BCa cells. However, owing to the limited association studies on p53 and USP28, more research is needed to determine the foundational processes. Taken together, USP28 is expected to be a prognostic marker for BCa (102,103).

Transforming growth factor- β (TGF- β) pathway. The TGF- β superfamily is the largest group of secreted growth factors, comprising several structurally and functionally related subfamilies, including TGF- β s, bone morphogenetic proteins, growth differentiation factors, mullerian inhibitor substance, activins and inhibins (104). It regulates several biological processes, including cell proliferation, differentiation, cell-cell interaction, immune regulation, extracellular matrix synthesis and inflammatory responses (105). All TGF- β and TGF- β -related family members bind to Type II receptors and recruit Type I receptors, which phosphorylate and activate Type I receptors (106). Type I receptors in turn phosphorylate and activate the downstream SMA and MAD-related protein (Smad)2 and Smad3. The C-terminally phosphorylated Smad2 and Smad3 recruit Smad4 to assemble into complexes and go into the nucleus to control TGF- β target gene transcription (107). In the nucleus, SMAD complexes activate specific genes through collaborative interactions with other DNA-binding and coactivator (or co-inhibitor) proteins (108).

TGF- β serves a dual role in tumorigenesis. During the early stages of tumor formation, TGF- β exerts its inhibitory effects primarily by inducing cell cycle arrest and activating the apoptotic pathways in cancer cells. However, as the tumor progresses, the suppressive effect of TGF- β on tumor cell proliferation diminishes or even disappears, leading to increased TGF- β secretion. Consequently, at this stage, TGF- β can act as a growth-promoting factor for tumor cells (Fig. 3) (109).

USP26. On the X chromosome, USP26 is expressed only in the testes of mice and humans and is believed to be a retrogene derived from autosomal USP39 (110). According to certain research, many cancers, including anaplastic thyroid carcinoma, CSCC and ESCC, express USP26 aberrantly (111-113). Analysis of USP26 expression in humanity extragonadal and testicular tissues revealed the varied roles of USP26 in cell differentiation and carcinogenesis (114). Mechanistically, Dirac and Bernards (115) reported that when USP26 was overexpressed, AR polyubiquitination was strongly inhibited, resulting in enhanced AR signaling. Notably, Cai *et al* (116) reported that androgen receptors (ARs) could block the TGF- β signaling pathway by directly acting on the substrate Smad3 via the TGF- β type I receptor. In conclusion, overexpression of USP26 can prevent PCa cells from proliferating and spreading.

MYC pathway. MYC is a prominent transcriptional regulator encompassing L-MYC, N-MYC and c-MYC, that are located on chromosomes 8, 2 and 1, respectively. The aberrant expression or activity of any members within this family has been demonstrated to play a role in tumor development. N-MYC and L-MYC exhibit tissue-specific expression patterns, primarily in the lung and nervous system (117). The N-terminal TAD, the MYC box domains (MB0-IV), the carboxy-terminus basic-helix-loop-helix-leucine zipper (bHLHZ), a PEST domain (rich in proline, glutamic acid, serine and threonine), and a NLS are the primary domains of MYC (118-122). The c-MYC oncogene signaling pathway regulates several biological processes including apoptotic cell death, proliferation, survival and differentiation (123). A number of upstream signaling routes, including the traditional PI3K/AKT/mTOR pathway can phosphorylate MYC protein, thereby enhancing

its DNA-binding ability (124). Subsequently, phosphorylated MYC forms a dimer with its natural ligand Max and initiates downstream DNA transcription to facilitate cellular growth and proliferation (125). Evidently, DUBs are engaged in the formation and development of urinary system neoplasms targeting the MYC signaling pathway, such as USP16 and USP43 (Fig. 2).

USP16. USP16 protein is a histone H2A-specific deubiquitination enzyme, and human chromosome 21 is home to its coding gene (126). USP16 is involved in the regulation of gene expression, cell-cycle progression and several other cellular functions (127). USP16 is abundantly expressed in many types of tumors originating from diverse tissues, such as gallbladder cancer, lung tumorigenesis, atherosclerosis and coronary artery diseases (128-130). Ge *et al* (131) reported that USP16 knockdown markedly inhibited PCa cell growth *in vitro* and *in vivo*. Mechanistically, the deubiquitination of USP16 stabilizes c-MYC to promote the initiation and progression of PCa. However, the specific mechanisms involved are not yet fully understood.

USP43. USP43 is a USP family member. The cDNA sequence of USP43 is 3,369 base pairs long and has an open reading frame that codes for a protein with 1,123 amino acids (132). Prior research reported that overexpression of USP43 could facilitate the growth of a number of malignancies, including CRC, BC, lung squamous cell carcinoma, PC and OS (133-137). USP43 deubiquitinates c-MYC at K148 and K289, primarily through deubiquitinase activity, which promotes BCa metastasis. The disruption of F-box and WD repeat domain containing 7 (FBXW7) accessibility and increased probability of interaction with c-MYC are caused by the overexpression of USP43 protein in BCa, thereby impeding c-MYC degradation (138). These findings imply that USP43 contributes to the growth of tumors in BCa and may serve as a marker for the eventual course of the disease.

Wnt/ β -catenin pathway. Wnt was initially derived from mouse breast cancer integrase-1 and *Drosophila* wingless. Considering the substantial functional protein similarities between these two genes, researchers opted to merge them, resulting in the designation of the Wnt gene (139). Wnt signaling is highly evolutionary conserved and serves a key role in organogenesis, tissue homeostasis, tissue regeneration and tumor formation (140). When Wnt ligands are not present, the destruction complex (DC) consisting of Axin/adematous polyposis coli (APC)/glycogen synthase kinase-3 β (GSK3 β)/casein kinase 1 α (CK1 α), then subsequently ubiquitinated by β -transducin repeat-containing protein (β -TrCP), which maintains the concentration of β -catenin in cells at a low level (141). When secreted Wnt ligands, such as Wnt3a and Wnt1, bind to Frizzled receptors and low-density lipoprotein receptor-related protein (LRP) co-receptors, LRP receptors are phosphorylated by CK1 α and GSK3 β , and disheveled protein is recruited to the plasma membrane and activated, leading to inactivation of the destruction complex DC. This stops β -catenin from constitutively degrading and from building up in the nucleus (142). In the nucleus, β -catenin activates Wnt-responsive gene transcription by dislocating the transducing-like enhancer protein (Groucho) complex and recruiting histone-modified coactivators, such as the CREB-binding protein/p300, brahma-related

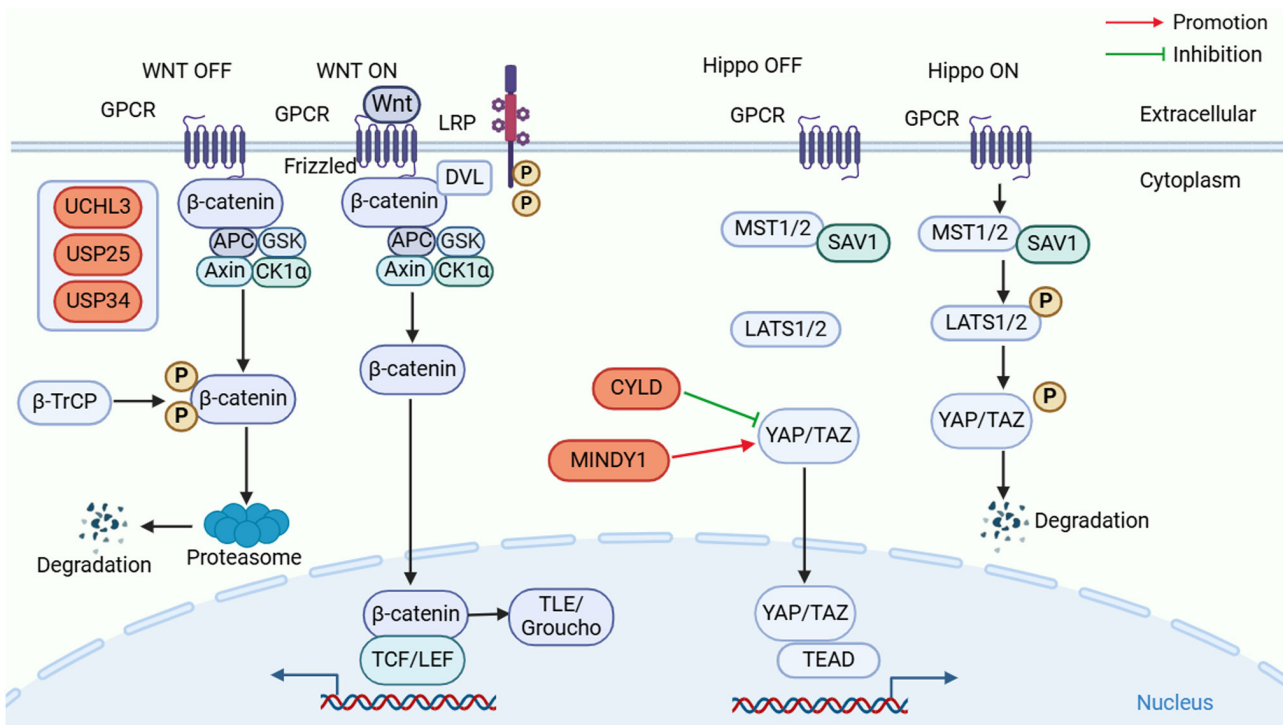


Figure 4. Role of DUBs in the Wnt/ β -catenin and Hippo pathways in urologic cancers. Wnt/ β -catenin pathway: The Wnt ligand is a glycoprotein that forms a complex by binding to the Frizzled receptor and LRP5/6. ZNRF3 and RNF43 ubiquitinate Frizzled receptors, whereas Respondin inhibits their activity and enhances the sensitivity of cells to Wnt. Upon Wnt activation, GSK-3 β dissociates from the APC/axin/GSK-3 β complex. In the absence of Wnt, β -catenin acts as a cell adhesion protein and transcriptional co-regulatory molecule that is degraded by β -TrCP/c after phosphorylation by CK1 and the APC/Axin/GSK-3 β complex. In the presence of Wnt, LRP5/6 forms a complex with Frizzled to activate DVL, leading to the displacement of GSK-3 β from APC/Axin. Stable β -catenin translocates into the nucleus, binds to LEF/TCF transcription factors and activates target gene transcription. USP34 promotes activation of the Wnt/ β -catenin pathway, but the specific mechanism has not yet been reported. Hippo pathway: Under normal circumstances, protein kinases such as MST1/2 and LATS1/2 exert inhibitory effects on the activity of YAP and TAZ in cells through phosphorylation, leading to their downregulation or absence. The upregulation of the Hippo signaling pathway promotes the activation of LATS kinase, which regulates gene expression by suppressing the activities of the transcriptional coactivators YAP and TAZ. When Hippo signaling is attenuated or molecules upstream of the pathway are mutated, the enhanced expression of YAP and TAZ facilitates uncontrolled cell proliferation. The CYLD protein can inhibit the ubiquitination of YAP and activate the expression of downstream ferroptosis-related factors ACSL4 and TFRC, thereby inhibiting the progression of PCa by promoting ferroptosis. MINDY1 binds to the YAP protein and increases its stability by eliminating the K48-linked ubiquitin chain. USP, ubiquitin-specific protease; GPCR, g-protein-coupled receptor; LRP, lipoprotein receptor-related protein; DVL, disheveled; APC, adenomatous polyposis coli; GSK3 β , glycogen synthase kinase-3 β ; CK1, casein kinase 1; LRP5/6, β -TrCP, β -transducin repeat-containing protein; LDL receptor-related proteins 5 and 6; ZNRF3, zinc and ring finger 3; RNF43, ring finger protein 43; TCF, T-cell factor; LEF, lymphoid enhancer-binding factor; MST1/2, mammalian Ste20-like kinases 1 and 2; SAV1, Salvador homolog-1; LATS1/2, large tumor suppressors 1 and 2; YAP, yes-associated protein 1; TAZ, transcriptional co-activator with PDZ-binding motif; TEAD, TEA domain; CYLD, lysine 63 deubiquitinase; ACSL4, acyl-CoA synthetase long-chain family 4; TFRC, transferrin 1 receptor.

gene 1, B-cell lymphoma 9 and pygopus to form active complexes with lymphoid enhancer-binding factor and T-cell factor proteins, stimulating the transcriptional activity of Wnt target genes and eliciting cellular reactions (143). The present section focusses on elucidating the role of DUBs in regulating the Wnt/ β -catenin pathway and exploring how dysregulation of this intricate network can contribute to the pathogenesis of tumors of the urinary system (Fig. 4).

Ubiquitin c-terminal hydrolase-13 (UCHL3). UCHL3, a cysteine protease, belongs to the UCH family and is a cysteine protease. The UCHL3 gene is located at 13q22.2 and consists of two main structures: A six-stranded antiparallel β -sheet and eight α -helices (144,145). Overexpression of UCHL3 has been reported in several cancers, including HCC, CESC, CRC and BCa (146-148). CTNNB1 is an important downstream transcriptional coactivator of the Wnt signaling pathway. In most malignant tumors, accumulation of CTNNB1 promotes Wnt/ β -catenin signaling, thereby promoting tumor progression (149). Liu *et al* (150) reported that overexpression of

UCHL3 was closely associated with proliferation, invasion and migration in BCa, and coimmunoprecipitation demonstrated that UCHL3 deubiquitinated and stabilized CTNNB1, which triggered the activation of the Wnt signaling pathway. These findings imply that UCHL3 contributes to the development of BCa in a pro-carcinogenic manner.

USP25. Full-length human USP25 contains 1,055 amino acids and is part of the USPs family. Structurally, USP25 has a classical structure similar to most USPs, including three substructural domains: Finger, palm and thumb (151). USP25 is involved in several cellular processes, including immune responses, inflammatory responses and metabolic regulation (152,153). In addition, there have been reports linking USP25 to malignant tumors, Alzheimer's disease and cardiomegaly (154,155). Tankyase (TNKS) is an important regulator of Wnt signaling. The TNKS anchor protein repeat sequences collaborate with the C-terminal peptide of USP25 to enhance the stability of TNKS and reduce the stability of AXIN1, thus promoting the Wnt/ β -catenin pathway.

Furthermore, Cheng *et al* (156) reported that selective inhibition of TNKS-USP25 intermolecular interactions was effective in inhibiting prostate tumor development, suggesting that the therapeutic exploitation of this inhibitor may provide opportunities for patients with Wnt pathway-dependent PCa.

USP34. In chromosome 2p15, there is a gene for USP34, a deubiquitinase belonging to the most extensive family of deubiquitinating enzymes (157). A number of diseases, such as cancer, gliomas and bone disease, are linked to USP dysregulation (158,159). USP34 serves a critical role in the Wnt signaling pathway, and it has been reported that the function of USP34 affects Axin degradation and β -catenin-mediated transcription (160). NanoRNAs, or small nucleolar RNAs, serve a role in the production of proteins and are associated with a number of illnesses, including cancer. Recently, a study reported that *SNORA70B* and its host gene *USP34* might directly regulate Wnt pathway to promote tumorigenesis in RCC. However, relevant proteins remain to be investigated (161).

Hippo pathway. The Hippo pathway was initially discovered in *Drosophila melanogaster* and serves as a pivotal regulator of tissue growth (162). A crucial function for dysregulation of Hippo signaling is served in the occurrence and development of malignancies, including carcinogenesis, cellular invasion, metastasis, maintenance of cancer cells and resistance to chemotherapy (163). The Hippo kinase cascade regulates tissue and organ size during development by phosphorylating the transcriptional coactivator yes-associated protein 1 (YAP). Activation of the Hippo pathway inhibits growth, whereas its inhibition promotes organ growth. Mechanistically, the mammalian Ste20-like kinase MST1/2 (Hippo kinase), with the help of adaptor Salvador homolog 1, phosphorylates the large tumor suppressor 1/2 kinases, which in turn phosphorylates the downstream YAP or the WW domain-containing transcription regulator 1 (164). Phosphorylated YAP attaches itself to the cytoplasm, where it is degraded and ubiquitinated, blocking the ability of YAP to stop apoptosis and promote cell proliferation (165). Nevertheless, YAP is able to reach the nucleus and bind to transcription factors when the Hippo pathway is suppressed, for example, TEA domain transcription factors, to promote the expression of target genes (Fig. 4) (166).

CYLD. CYLD may promote the NF- κ B pathway by activating NF- κ B/p65 and acting as a potential tumor suppressor in BCa (55). Notably, Gu *et al* (167) reported that the CYLD protein upregulates the levels of downstream ferroptosis-related proteins acyl-CoA synthetase long chain family member 4 and transferrin receptor whilst inhibiting the ubiquitination of YAP, inhibiting PCa progression by promoting ferroptosis. These findings may contribute to a more profound understanding of the molecular mechanisms underlying PCa, thereby facilitating enhanced therapeutic strategies for ferroptosis.

Motif interacting with ubiquitin-containing novel DUB family-1 (MINDY1). MINDY1, also known as FAM63A, belongs to a crucial member of DUBs. It contains a Ub binding domain (UBD) that can bind K48-linked polyUb chains and an unknown functional domain (DUF544) (168). Previous studies have reported that MINDY1 is abnormally highly expressed in BC and HCC (169,170). The novel key regulator

MINDY1 serves a crucial role in maintaining stem cell self-renewal by enhancing the stability of core self-renewal proteins (171). According to Luo *et al* (172), MINDY1 may encourage the growth of BCa cells both *in vivo* and *in vitro*. It has been reported that MINDY1 binds to YAP and increases its stability by eliminating the K48-linked ubiquitin ring from YAP, indicating that it may be a potential target for the intervention of BCa.

Other DUBs

USP10. The AR signaling pathway serves an important role in all phases of prostate carcinogenesis (173). USP10 is a multi-functional deubiquitinating enzyme located on chromosome 16q24.1, which serves an important role in several signaling pathways, including the p53, mTOR and AR signaling pathway (174-176). In the regulation of gene transcription, H2A is a core histone. It was reported that USP10 mediates the activation of the AR signaling pathway by deubiquitinating and stabilizing H2A. It is also able to deubiquitinate H2A.Z (H2A mutant), which is able to bind to enhancers and promoters that bind to PSA and kallikrein-like 2 genes, and thus is involved in the regulation of the AR pathway (177).

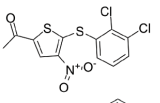
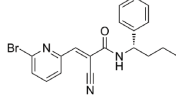
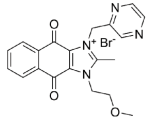
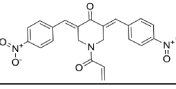
USP21. USP21 is located on chromosome 1q23.3 and is a member of the USP family (178). The structure of USP21 is comparatively simple, comprising a catalytic structural area at the C-terminal and a disordered N-terminal section (179). USP21 is essential for DNA damage repair and viral immunity, and tumor progression, by deubiquitinating different proteins, making USP21 a potential target for tumor therapy (180,181). Chen *et al* (182) reported that USP21 is upregulated in BCa and is associated with tumor invasion and metastasis. Research has also indicated that patients who exhibit high levels of USP21 are less likely to survive. Mechanistically, USP21 regulates certain proteins that affect cell proliferation via deubiquitination, for instance, enhancer of zeste homolog 2 (EZH2), thus promoting tumor development (182).

USP22. USP22 is widely expressed in mammals and is found on the long limb of chromosome 17 in the human genome. It comprises 13 exons and has a cDNA with 1,578 base pairs. USP22 inhibits protein breakdown by deubiquitinating substrate proteins, which is how it regulates gene transcription, injury to DNA repair and immune escape (183,184). It was reported that USP22 expression is markedly elevated in malignant tumors, such as HCC, NSCLC and CC, indicating that it may be a significant pro-carcinogenic factor (185-187). In BCa, high expression of USP22 was detected, which was inhibited by transfection of 15/21 asymmetric interfering RNA, which specifically targets USP22, leading to EJ cell cycle arrest and inhibition of cell proliferation (188). Similarly, USP22 is a crucial biological target and AR regulator in PCa. USP22 not only controls PCa advances as AR accumulation and signaling but also stabilizes MYC expression in cancer cells but also accelerates its growth. In conclusion, USP22 may offer a new viewpoint on the care of patients with urological tumors (189,190).

3. Targeting therapy for urologic cancers

Urologic cancers are one of the common cancers with a marked increase of incidence in recent years. Traditional treatment

Table II. Summary of inhibitors targeting the deubiquitylating enzymes in urologic cancers.

First author/s, year	Target	Drug	Molecular formula	Molecular structure	Mechanism of action	(Refs.)
Lee <i>et al.</i> , 2020	USP7	P5091	C ₁₂ H ₇ Cl ₂ NO ₃ S ₂		Inhibit cell proliferation, clone formation and migration of PCa	(193)
Wang <i>et al.</i> , 2014	USP9X	WP1130	C ₁₉ H ₁₈ BrN ₃ O		Inhibit the growth of PCa	(196)
Sim <i>et al.</i> , 2018	CYLD	YM155	C ₂₀ H ₁₉ BrN ₄ O ₃		Inhibit the growth of RCC/PCa	(54)
Chow <i>et al.</i> , 2022	UCHL5	b-AP15	C ₂₂ H ₁₇ N ₃ O ₆		Decrease the viability and induce apoptosis of BCa	(201)

USP, ubiquitin-specific protease; DUB, deubiquitylating enzymes; CYLD, lysine 63 deubiquitinase; UCHL5, ubiquitin C-terminal hydrolase L5; RCC, renal cell carcinoma; PCa, prostate cancer; BCa, bladder cancer.

options mainly include surgical resection, chemotherapy, radiotherapy, immunotherapy and hormonal therapy. Early surgical resection is an effective therapeutic maneuver, but the majority of patients still die of recurrence and metastasis; therefore, it is important to discover new therapeutic strategies (191). DUBs can regulate the levels of proteins that are not responsive or directly inhibited by conventional targeted therapies, including targets that are not patentable. Examples of these potential targets include transcription factors, drug-resistant enzymes and proteins involved in protein interactions that lack distinctive features and pose challenges for intervention with small molecules (192). Given the important role of DUBs in cancer development, the present review summarizes the inhibitors targeting DUBs.

DUB inhibitors. USP7 is currently one of the most extensively studied DUBs, and several inhibitors have been developed based on its pivotal role in the p53 pathway (22). P5091, an inhibitor of USP7, can prevent PCa cells from migrating, invading and creating spheres, especially in combination with EZH2 inhibitors. The decrease in PCa cells count induced by P5091 treatment is attributed, at least partially, to apoptosis mediated by caspases (193). P22077 has been reported to induce apoptosis in HCC and PC, which is expected to be a promising target for the treatment of PCa (194,195). DUB inhibitors P22077 and P50429 covalently modify USP7, leading to cysteine catalysis and inducing conformational changes in enzymes associated with active site rearrangement, thereby resulting in the inhibition of enzyme activity (196). In recent years, researchers have also developed a new generation of allosteric inhibitors, such as XL188 and FT671, which can co-crystallize with the catalytic core of USP7 (197,198). ETS-related gene (ERG) is a proto-oncogene and a member of the E-twenty-six transcription factor family, which is overexpressed in 40% of patients with PCa. WP1130 is an inhibitor of USP9X and has been reported to degrade ERG, resulting in the blockage of PCa-related gene expression and inhibition of tumor progression (196).

Prior research has demonstrated the effectiveness of YM155, an inhibitor of survivin in small molecules, in reducing the viability of RCC cells generated from patients and immortalized cells. By activating the deubiquitinating enzyme CYLD, it results in IKK β inhibition, I κ B α stabilization, as well as the cytosolic persistence of NF- κ B heterodimers. As a result, transcription of the NF- κ B target gene survivin is reduced (54). Xu *et al.* (199) reported that YM155 inhibited survivin *in vitro* and *in vivo* human hormone-refractory PCa cells and demonstrated potent antitumor activity. Moderate single-agent activity was also reported in a phase I study in a large number of previously treated patients. Furthermore, a phase II study of YM155 in combination with docetaxel for castration-resistant PCa reported that YM155 showed good activity (study ID no. NCT00514267) (200). b-AP15, an inhibitor of UCHL5, can enhance the accumulation of polyubiquitinated proteins and subsequent endoplasmic reticulum stress, thereby decreasing BCa cell viability and inducing apoptosis. In addition, Chow *et al.* (201) reported that a combination of b-AP15 and cisplatin showed better therapeutic efficacy than monotherapy (Table II).

In summary, the AR and p53 pathways are considered as the primary signaling pathways in PCa, with USP7 emerging as a promising therapeutic target due to its extensive drug development. Currently, there is a lack of reported information regarding the key signaling pathways involved in DUBs in RCC and BCa. Nevertheless, CYLD and UCHL5 are likely to be pivotal DUBs in RCC and BCa respectively, given their ongoing development of relevant inhibitors. Facilitating the advancement of DUB inhibitors and commencing clinical trials necessitates multifaceted endeavors and collaboration. By enhancing fundamental research, devising efficient screening and validation technologies, fostering interdisciplinary cooperation, promoting clinical trials and reinforcing international cooperation and exchanges, it is anticipated that the development process of DUBs inhibitors will be expedited along with their early implementation in clinical therapy.

Other inhibitors. AR, a member of the steroid hormone receptor family, is expressed in PCa and BCa (202). When androgens bind to AR, the AR is released and translocated into the nucleus, thus promoting gene transcription and accelerating tumor progression. Therefore, inhibitors targeting the AR signaling pathway are important therapeutic approaches for such patients (203). Bicalutamide is an androgen receptor blocker that blocks testosterone production, thereby decreasing hormone levels and inhibiting the growth and proliferation of PCa cells (204). Apalutamide is a second-generation nonsteroidal AR inhibitor currently used for the treatment of PCa. Mechanistically, it can successfully stop androgens from binding to the receptor and from transferring AR into the nucleus of tumor cells, and serve a role in inhibiting the growth of tumor cells (205). Enzalutamide is an AR antagonist that exhibits substantial improvement in metastatic hormone-sensitive PCa, much like apalutamide does (206). Abiraterone is an androgen synthesis inhibitor that blocks CYP17-mediated androgen production, thereby inhibiting the growth of PCa cells (207).

The primary mechanism of action for immune checkpoint inhibitors (ICIs) is the blockade of inhibitory signaling pathways within the immune system, thereby reinvigorating the recognition and cytotoxicity capabilities of immune cells, such as T cells, towards tumor cells. In urinary system cancer, key targets for this drug class encompass programmed death protein 1 (PD-1) and its ligand (PD-L1), as well as cytotoxic T lymphocyte-associated antigen 4. The US Food and Drug Administration has thus far granted approval for three PD-L1 inhibitors (atezolizumab, avelumab and durvalumab) in the treatment of urothelial cancer (208). PD-1 drugs have been approved for the treatment of patients with advanced BCa and RCC, notably improving patient survival and quality of life (209). A recent study by Kuang *et al* (210) reported that Thr288, Arg292 and Asp293 of USP2 bind to PD-L1 through the resolution of K48 link polyubiquitination at the PD-L1 lysine 270 site. USP2 depletion led to endoplasmic reticulum-related degradation of PD-L1, which weakened PD-L1/PD-1 interactions and sensitivities T cells to cancer cells.

Tyrosine kinase inhibitors (TKIs) block the signal transduction pathway of tumor cells by binding to the kinase domain of their target RTK, thereby inhibiting the proliferation, invasion and metastasis of tumor cells. The combination of TKIs and ICIs is considered a primary treatment option for patients with advanced RCC (211). The latest research findings indicate that cabozantinib has an impact on the tumor microenvironment and reinstates T cells activity, thereby suggesting that its combination therapy with ICIs could potentially synergistically target the growth of both primary and metastatic PCa (212). McCann *et al* (213) reported that the deletion of USP17 in EGFR WT NSCLC cells, when combined with EGFR TKI treatment, resulted in apoptosis induction. This suggests that targeting USP17 could enhance therapeutic efficacy and broaden the patient population responsive to these drugs. However, there are no reports of DUBs and TKIs in urinary system tumors, to the best of our knowledge.

Rapamycin is a first-generation mTOR inhibitor that selectively inhibit the activity of mTOR by binding to

FK506-binding protein-12 and forming ternary complexes with mTOR (214). Everolimus and temsirolimus are used for advanced and metastatic kidney cancer (215,216) and the efficacy of everolimus in the treatment of kidney cancer has been demonstrated by the RECORD-1 study (217). The application of mTOR inhibitors in urinary system tumors is primarily focused on the treatment of RCC, and has demonstrated marked efficacy. Notably, Roldán-Romero *et al* (218) reported that the involvement of USP9X in the regulation of p62-mediated autophagy through ubiquitination potentially led to chromophobe renal cell carcinoma cells sensitization to temsirolimus due to the ablation of USP9X. This also suggests the administration of mTOR inhibitors presents a potential therapeutic avenue for tumors harboring USP9X mutations. Simultaneously, its research and utilization in other urologic cancers are progressively expanding.

4. Conclusions and perspectives

Men are more likely to acquire cancers of the urinary system, such as RCC, PCa and BCa, than women. Conventional surgery, chemotherapy and radiotherapy can only enhance the quality of life of patients but cannot significantly improve their survival time. The occurrence of these tumors is associated with several factors, among which gene mutations and abnormal gene expression serve a crucial role. Deubiquitinating enzymes regulate protein ubiquitination levels and participate in cell cycle regulation, signal transduction pathways and gene transcription processes, thereby influencing tumor initiation and progression. Previous studies have indicated that certain deubiquitinating enzymes exhibit aberrant expression patterns in urological tumors. Such dysregulation may lead to uncontrolled cell proliferation and impaired apoptosis mechanisms that promote tumor formation and advancement. Furthermore, deubiquitinating enzymes may interact with other genes or signaling pathways related to tumorigenesis. The present review focused on the regulation of deubiquitinating enzymes in several signaling pathways, including the PI3K/AKT, NF- κ B, RAS/RAF/MEK/ERK, p53, TGF- β , MYC, Wnt/ β -catenin and Hippo pathways.

USP7, USP9X and UCHL5 were explored as possible therapeutic focal points in the context of specific treatment for urologic tumors. Nonetheless, the development of DUB inhibitors is in the preliminary phase, with numerous unresolved queries. As an illustration, the specific substrates and subsequent effectors of certain DUBs in several pathways remain unidentified, encompassing the RAS/RAF/MEK/ERK pathway, the Wnt/ β -catenin pathway and others. Despite these advances, much remains unknown regarding the mechanism of deubiquitination in urologic tumors. In summary, the mechanism of deubiquitinating enzymes in urologic tumors remains to be further studied; however, they have shown promise as potential targets for cancer treatment and prognosis evaluation. In order to provide new ideas and approaches for the clinical treatment of urinary system malignancies, future research should concentrate on elucidating the specifics of the mechanism of action and creating tailored therapy techniques.

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Authors' contributions

LW conceptualized the study, wrote original draft, wrote the review and edited the manuscript. JW and LC conceptualized the study, wrote the review and edited the manuscript. XJ and JC revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 71: 209-249, 2021.
- Nguyen-Nielsen M and Borre M: Diagnostic and Therapeutic Strategies for Prostate Cancer. *Semin Nucl Med* 46: 484-490, 2016.
- Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M and Mafakher L: Renal cell carcinoma: An overview of the epidemiology, diagnosis, and treatment. *G Ital Nefrol* 39: 2022-vol3, 2022.
- Lenis AT, Lec PM, Chamie K and Mshs MD: Bladder Cancer: A Review. *JAMA* 324: 1980-1991, 2020.
- Gao H, Yin J, Ji C, Yu X, Xue J, Guan X, Zhang S, Liu X, Xing F: Targeting ubiquitin specific proteases (USPs) in cancer immunotherapy: From basic research to preclinical application. *J Exp Clin Cancer Res* 42: 225, 2023.
- Zheng LL, Wang LT, Pang YW, Sun LP and Shi L: Recent advances in the development of deubiquitinases inhibitors as antitumor agents. *Eur J Med Chem* 266: 116161, 2024.
- Popovic D, Vucic D and Dikic I: Ubiquitination in disease pathogenesis and treatment. *Nat Med* 20: 1242-1253, 2014.
- Dagar G, Kumar R, Yadav KK, Singh M and Pandita TK: Ubiquitination and deubiquitination: Implications on cancer therapy. *Biochim Biophys Acta Gene Regul Mech* 1866: 194979, 2023.
- Han S, Wang R, Zhang Y, Li X, Gan Y, Gao F, Rong P, Wang W and Li W: The role of ubiquitination and deubiquitination in tumor invasion and metastasis. *Int J Biol Sci* 18: 2292-2303, 2022.
- Ye Z, Yang J, Jiang H and Zhan X: The roles of protein ubiquitination in tumorigenesis and targeted drug discovery in lung cancer. *Front Endocrinol (Lausanne)* 14: 1220108, 2023.
- Zhou Z, Zheng K, Zhou S, Yang Y, Chen J and Jin X: E3 ubiquitin ligases in nasopharyngeal carcinoma and implications for therapies. *J Mol Med (Berl)* 101: 1543-1565, 2023.
- Dewson G, Eichhorn PJA and Komander D: Deubiquitinases in cancer. *Nat Rev Cancer* 23: 842-862, 2023.
- Coutte L, Dreyer C, Sablin MP, Faivre S and Raymond E: PI3K-AKT-mTOR pathway and cancer. *Bull Cancer* 99: 173-180, 2012 (In French).
- Cantley LC: The phosphoinositide 3-kinase pathway. *Science* 296: 1655-1657, 2002.
- Vanhaesebroeck B, Whitehead MA and Piñeiro R: Molecules in medicine mini-review: Isoforms of PI3K in biology and disease. *J Mol Med (Berl)* 94: 5-11, 2016.
- Gagliardi PA, Puliafito A and Primo L: PDK1: At the crossroad of cancer signaling pathways. *Semin Cancer Biol* 48: 27-35, 2018.
- Tan AC: Targeting the PI3K/Akt/mTOR pathway in non-small cell lung cancer (NSCLC). *Thorac Cancer* 11: 511-518, 2020.
- Yu Z, Li H, Zhu J, Wang H and Jin X: The roles of E3 ligases in Hepatocellular carcinoma. *Am J Cancer Res* 12: 1179-1214, 2022.
- Ngeow J and Eng C: PTEN in Hereditary and Sporadic Cancer. *Cold Spring Harb Perspect Med* 10: a036087, 2020.
- Noorolyai S, Shajari N, Baghbani E, Sadreddini S and Baradaran B: The relation between PI3K/AKT signalling pathway and cancer. *Gene* 698: 120-128, 2019.
- Christine A, Park MK, Song SJ and Song MS: The equilibrium of tumor suppression: DUBs as active regulators of PTEN. *Exp Mol Med* 54: 1814-1821, 2022.
- Saha G, Roy S, Basu M and Ghosh MK: USP7-a crucial regulator of cancer hallmarks. *Biochim Biophys Acta Rev Cancer* 1878: 188903, 2023.
- Pozhidaeva A and Bezsonova I: USP7: Structure, substrate specificity, and inhibition. *DNA Repair (Amst)* 76: 30-39, 2019.
- Song MS, Salmena L, Carracedo A, Egia A, Lo-Coco F, Teruya-Feldstein J and Pandolfi PP: The deubiquitylation and localization of PTEN are regulated by a HAUSP-PML network. *Nature* 455: 813-817, 2008.
- Wang Q, Sun Z, Xia W, Sun L, Du Y, Zhang Y and Jia Z: Role of USP13 in physiology and diseases. *Front Mol Biosci* 9: 977122, 2022.
- Jin J, He J, Li X, Ni X and Jin X: The role of ubiquitination and deubiquitination in PI3K/AKT/mTOR pathway: A potential target for cancer therapy. *Gene* 889: 147807, 2023.
- Cui X, Yu H, Yao J, Li J, Li Z and Jiang Z: ncRNA-mediated overexpression of ubiquitin-specific proteinase 13 contributes to the progression of prostate cancer via modulating AR signaling, DNA damage repair and immune infiltration. *BMC Cancer* 22: 1350, 2022.
- Zhao Y, Zhang B, Lei Y, Sun J, Zhang Y, Yang S and Zhang X: Knockdown of USP39 induces cell cycle arrest and apoptosis in melanoma. *Tumour Biol* 37: 13167-13176, 2016.
- Yuan J, Li X, Zhang G, Cheng W, Wang W, Lei Y, Ma Q and Song G: USP39 mediates p21-dependent proliferation and neoplasia of colon cancer cells by regulating the p53/p21/CDC2/cyclin B1 axis. *Mol Carcinog* 60: 265-278, 2021.
- Yuan X, Sun X, Shi X, Jiang C, Yu D, Zhang W, Guan W, Zhou J, Wu Y, Qiu Y and Ding Y: USP39 promotes the growth of human hepatocellular carcinoma in vitro and in vivo. *Oncol Rep* 34: 823-832, 2015.
- An Y, Yang S, Guo K, Ma B and Wang Y: Reduced USP39 expression inhibits malignant proliferation of medullary thyroid carcinoma in vitro. *World J Surg Oncol* 13: 255, 2015.
- Li KY, Zhang J, Jiang LC, Zhang B, Xia CP, Xu K, Chen HY, Yang QZ, Liu SW and Zhu H: Knockdown of USP39 by lentivirus-mediated RNA interference suppresses the growth of oral squamous cell carcinoma. *Cancer Biomark* 16: 137-144, 2016.
- Xing Z, Sun F, He W, Wang Z, Song X and Zhang F: Downregulation of ubiquitin-specific peptidase 39 suppresses the proliferation and induces the apoptosis of human colorectal cancer cells. *Oncol Lett* 15: 5443-5450, 2018.
- Xu Y, Zhu MR, Zhang JY, Si GM and Lv JJ: Knockdown of ubiquitin-specific peptidase 39 inhibits the malignant progression of human renal cell carcinoma. *Mol Med Rep* 17: 4729-4735, 2018.

35. Rolén U, Kobzeva V, Gasparjan N, Ovaa H, Winberg G, Kisseljov F and Masucci MG: Activity profiling of deubiquitinating enzymes in cervical carcinoma biopsies and cell lines. *Mol Carcinog* 45: 260-269, 2006.
36. Chen Y, Fu D, Xi J, Ji Z, Liu T, Ma Y, Zhao Y, Dong L, Wang Q and Shen X: Expression and clinical significance of UCH37 in human esophageal squamous cell carcinoma. *Dig Dis Sci* 57: 2310-2317, 2012.
37. Wang L, Chen YJ, Xu K, Wang YY, Shen XZ and Tu RQ: High expression of UCH37 is significantly associated with poor prognosis in human epithelial ovarian cancer. *Tumour Biol* 35: 11427-11433, 2014.
38. Chen Z, Niu X, Li Z, Yu Y, Ye X, Lu S and Chen Z: Effect of ubiquitin carboxy-terminal hydrolase 37 on apoptotic in A549 cells. *Cell Biochem Funct* 29: 142-148, 2011.
39. Cutts AJ, Soond SM, Powell S and Chantray A: Early phase TGF β receptor signalling dynamics stabilised by the deubiquitinase UCH37 promotes cell migratory responses. *Int J Biochem Cell Biol* 43: 604-612, 2011.
40. Cao Y, Yan X, Bai X, Tang F, Si P, Bai C, Tuoheti K, Guo L, Yisha Z, Liu T and Liu T: UCHL5 Promotes Proliferation and Migration of Bladder Cancer Cells by Activating c-Myc via AKT/mTOR Signaling. *Cancers (Basel)* 14: 5538, 2022.
41. Oeckinghaus A, Hayden MS and Ghosh S: Crosstalk in NF- κ B signaling pathways. *Nat Immunol* 12: 695-708, 2011.
42. Lawrence T: The nuclear factor NF- κ B pathway in inflammation. *Cold Spring Harb Perspect Biol* 1: a001651, 2009.
43. Gilmore TD: Introduction to NF- κ B: Players, pathways, perspectives. *Oncogene* 25: 6680-6684, 2006.
44. Hayden MS and Ghosh S: Shared principles in NF- κ B signaling. *Cell* 132: 344-362, 2008.
45. Au PY and Yeh WC: Physiological roles and mechanisms of signaling by TRAF2 and TRAF5. *Adv Exp Med Biol* 597: 32-47, 2007.
46. Zhang W, Zhang X, Wu XL, He LS, Zeng XF, Crammer AC and Lipsky PE: Competition between TRAF2 and TRAF6 regulates NF- κ B activation in human B lymphocytes. *Chin Med Sci J* 25: 1-12, 2010.
47. Liu H, Zeng L, Yang Y, Guo C and Wang H: Bcl-3: A Double-Edged Sword in Immune Cells and Inflammation. *Front Immunol* 13: 847699, 2022.
48. Franzoso G, Bours V, Azarenko V, Park S, Tomita-Yamaguchi M, Kanno T, Brown K and Siebenlist U: The oncoprotein Bcl-3 can facilitate NF- κ B-mediated transactivation by removing inhibiting p50 homodimers from select κ B sites. *EMBO J* 12: 3893-3901, 1993.
49. Fujita T, Nolan GP, Liou HC, Scott ML and Baltimore D: The candidate proto-oncogene bcl-3 encodes a transcriptional coactivator that activates through NF- κ B p50 homodimers. *Genes Dev* 7: 1354-1363, 1993.
50. Tang W, Wang H, Claudio E, Tassi I, Ha HL, Saret S and Siebenlist U: The oncoprotein and transcriptional regulator Bcl-3 governs plasticity and pathogenicity of autoimmune T cells. *Immunity* 41: 555-566, 2014.
51. Marín-Rubio JL, Raote I, Inns J, Dobson-Stone C and Rajan N: CYLD in health and disease. *Dis Model Mech* 16: dmm050093, 2023.
52. Mathis BJ, Lai Y, Qu C, Janicki JS and Cui T: CYLD-mediated signaling and diseases. *Curr Drug Targets* 16: 284-294, 2015.
53. Massoumi R: CYLD: A deubiquitination enzyme with multiple roles in cancer. *Future Oncol* 7: 285-297, 2011.
54. Sim MY, Yuen JSP and Go ML: Anti-survivin effect of the small molecule inhibitor YM155 in RCC cells is mediated by time-dependent inhibition of the NF- κ B pathway. *Sci Rep* 8: 10289, 2018.
55. Yuan H, Wei S, Ren Z, Li F, Liu B, Liu R and Zhang X: KLHL21/CYLD signaling confers aggressiveness in bladder cancer through inactivating NF- κ B signaling. *Int Immunopharmacol* 114: 109202, 2023.
56. Man X, Piao C, Lin X, Kong C, Cui X and Jiang Y: USP13 functions as a tumor suppressor by blocking the NF- κ B-mediated PTEN downregulation in human bladder cancer. *J Exp Clin Cancer Res* 38: 259, 2019.
57. Man X, Piao C, Lin X, Kong C, Cui X and Jiang Y: Correction to: USP13 functions as a tumor suppressor by blocking the NF- κ B-mediated PTEN downregulation in human bladder cancer. *J Exp Clin Cancer Res* 40: 386, 2021.
58. Yang GF, Zhang X, Su YG, Zhao R and Wang YY: The role of the deubiquitinating enzyme DUB3/USP17 in cancer: A narrative review. *Cancer Cell Int* 21: 455, 2021.
59. Han L, Yang J, Wang X, Wu Q, Yin S, Li Z, Zhang J, Xing Y, Chen Z, Tsun A, *et al*: The E3 deubiquitinase USP17 is a positive regulator of retinoic acid-related orphan nuclear receptor γ t (ROR γ t) in Th17 cells. *J Biol Chem* 289: 25546-25555, 2014.
60. Haq S and Ramakrishna S: Deubiquitylation of deubiquitylases. *Open Biol* 7: 170016, 2017.
61. Baohai X, Shi F and Yongqi F: Inhibition of ubiquitin specific protease 17 restrains prostate cancer proliferation by regulation of epithelial-to-mesenchymal transition (EMT) via ROS production. *Biomed Pharmacother* 118: 108946, 2019.
62. Fang JY and Richardson BC: The MAPK signalling pathways and colorectal cancer. *Lancet Oncol* 6: 322-327, 2005.
63. Guo YJ, Pan WW, Liu SB, Shen ZF, Xu Y and Hu LL: ERK/MAPK signalling pathway and tumorigenesis. *Exp Ther Med* 19: 1997-2007, 2020.
64. Santarpia L, Lippman SM and El-Naggar AK: Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. *Expert Opin Ther Targets* 16: 103-119, 2012.
65. Wu PK, Becker A and Park JJ: Growth Inhibitory Signaling of the Raf/MEK/ERK Pathway. *Int J Mol Sci* 21: 5436, 2020.
66. Maik-Rachline G, Hacohen-Lev-Ran A and Seger R: Nuclear ERK: Mechanism of Translocation, Substrates, and Role in Cancer. *Int J Mol Sci* 20: 1194, 2019.
67. Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, Dimitriadou S, Liu DL, Kantheti HS, Saghatian S, *et al*: Oncogenic signaling pathways in the cancer genome atlas. *Cell* 173: 321-337.e10, 2018.
68. Zhang J, Wang J, Luan T, Zuo Y, Chen J, Zhang H, Ye Z, Wang H and Hai B: Deubiquitinase USP9X regulates the invasion of prostate cancer cells by regulating the ERK pathway and mitochondrial dynamics. *Oncol Rep* 41: 3292-3304, 2019.
69. Hu W, Su Y, Fei X, Wang X, Zhang G, Su C, Du T, Yang T, Wang G, Tang Z and Zhang J: Ubiquitin specific peptidase 19 is a prognostic biomarker and affect the proliferation and migration of clear cell renal cell carcinoma. *Oncol Rep* 43: 1964-1974, 2020.
70. Meng Y, Hong C, Yang S, Qin Z, Yang L and Huang Y: Roles of USP9X in cellular functions and tumorigenesis (Review). *Oncol Lett* 26: 506, 2023.
71. Wan YF, Zhang CY, Cheng XW, Liu LS, Zhou T, Gao JK, Zhu HQ and Liu YH: USP9X expression is functionally related to laryngeal cancer. *J Cancer* 14: 591-599, 2023.
72. Jaiswal A, Murakami K, Elia A, Shibahara Y, Done SJ, Wood SA, Donato NJ, Ohashi PS and Reedijk M: Therapeutic inhibition of USP9x-mediated Notch signaling in triple-negative breast cancer. *Proc Natl Acad Sci USA* 118: e2101592118, 2021.
73. Jie X, Fong WP, Zhou R, Zhao Y, Zhao Y, Meng R, Zhang S, Dong X, Zhang T, Yang K, *et al*: USP9X-mediated KDM4C deubiquitination promotes lung cancer radioresistance by epigenetically inducing TGF- β 2 transcription. *Cell Death Differ* 28: 2095-2111, 2021.
74. Zhu Y, Gu L, Lin X, Zhou X, Lu B, Liu C, Lei C, Zhou F, Zhao Q, Prochownik EV and Li Y: USP19 exacerbates lipogenesis and colorectal carcinogenesis by stabilizing ME1. *Cell Rep* 37: 110174, 2021.
75. Lee JG, Kim W, Gygi S and Ye Y: Characterization of the deubiquitinating activity of USP19 and its role in endoplasmic reticulum-associated degradation. *J Biol Chem* 289: 3510-3517, 2014.
76. Dong Z, Guo S, Wang Y, Zhang J, Luo H, Zheng G, Yang D, Zhang T, Yan L, Song L, *et al*: USP19 Enhances MMP2/MMP9-Mediated tumorigenesis in gastric cancer. *Oncotargets Ther* 13: 8495-8510, 2020.
77. Tyagi A, Karapurkar JK, Colaco JC, Sarodaya N, Antao AM, Kaushal K, Haq S, Chandrasekaran AP, Das S, Singh V, *et al*: USP19 Negatively Regulates p53 and promotes cervical cancer progression. *Mol Biotechnol* 66: 2032-2045, 2024.
78. Li X, Yuan J, Song C, Lei Y, Xu J, Zhang G, Wang W and Song G: Deubiquitinase USP39 and E3 ligase TRIM26 balance the level of ZEB1 ubiquitination and thereby determine the progression of hepatocellular carcinoma. *Cell Death Differ* 28: 2315-2332, 2021.
79. Zhu X, Ma J, Lu M, Liu Z, Sun Y and Chen H: The Deubiquitinase USP39 promotes esophageal squamous cell carcinoma malignancy as a splicing factor. *Genes (Basel)* 13: 819, 2022.
80. Zhang Z, Liu W, Bao X, Sun T, Wang J, Li M and Liu C: USP39 facilitates breast cancer cell proliferation through stabilization of FOXM1. *Am J Cancer Res* 12: 3644-3661, 2022.

81. Yuan J, Li X, Zhang Y, Zhang G, Cheng W, Wang W, Lei Y and Song G: USP39 attenuates the antitumor activity of cisplatin on colon cancer cells dependent on p53. *Cell Biol Toxicol* 39: 1995-2010, 2023.
82. Huang J: Current developments of targeting the p53 signaling pathway for cancer treatment. *Pharmacol Ther* 220: 107720, 2021.
83. Joerger AC and Fersht AR: The p53 Pathway: Origins, inactivation in cancer, and emerging therapeutic approaches. *Annu Rev Biochem* 85: 375-404, 2016.
84. Lahalle A, Lacroix M, De Blasio C, Cissé MY, Linares LK and Le Cam L: The p53 pathway and metabolism: The tree that hides the forest. *Cancers (Basel)* 13: 133, 2021.
85. Zhao Y, Yu H and Hu W: The regulation of MDM2 oncogene and its impact on human cancers. *Acta Biochim Biophys Sin (Shanghai)* 46: 180-189, 2014.
86. Kwon SK, Saindane M and Baek KH: p53 stability is regulated by diverse deubiquitinating enzymes. *Biochim Biophys Acta Rev Cancer* 1868: 404-411, 2017.
87. Klein AM, de Queiroz RM, Venkatesh D and Prives C: The roles and regulation of MDM2 and MDMX: It is not just about p53. *Genes Dev* 35: 575-601, 2021.
88. Ren Y, Zhao P, Liu J, Yuan Y, Cheng Q, Zuo Y, Qian L, Liu C, Guo T, Zhang L, *et al*: Deubiquitinase USP2a sustains interferons antiviral activity by restricting ubiquitination of activated STAT1 in the Nucleus. *PLoS Pathog* 12: e1005764, 2016.
89. Li Y, He X, Wang S, Shu HB and Liu Y: USP2a positively regulates TCR-induced NF- κ B activation by bridging MALT1-TRAF6. *Protein Cell* 4: 62-70, 2013.
90. Allende-Vega N, Sparks A, Lane DP and Saville MK: MdmX is a substrate for the deubiquitinating enzyme USP2a. *Oncogene* 29: 432-441, 2010.
91. Xiong B, Huang J, Liu Y, Zou M, Zhao Z, Gong J, Wu X and Qiu C: Ubiquitin-specific protease 2a promotes hepatocellular carcinoma progression via deubiquitination and stabilization of RAB1A. *Cell Oncol (Dordr)* 44: 329-343, 2021.
92. Selvendiran K, Ahmed S, Dayton A, Ravi Y, Kuppusamy ML, Bratasz A, Rivera BK, Kálai T, Hideg K and Kuppusamy P: HO-3867, a synthetic compound, inhibits the migration and invasion of ovarian carcinoma cells through downregulation of fatty acid synthase and focal adhesion kinase. *Mol Cancer Res* 8: 1188-1197, 2010.
93. Kim J, Keay SK, You S, Loda M and Freeman MR: A synthetic form of frizzled 8-associated antiproliferative factor enhances p53 stability through USP2a and MDM2. *PLoS One* 7: e50392, 2012.
94. Stevenson LF, Sparks A, Allende-Vega N, Xirodimas DP, Lane DP and Saville MK: The deubiquitinating enzyme USP2a regulates the p53 pathway by targeting Mdm2. *EMBO J* 26: 976-986, 2007.
95. Ballar Kirmizibayrak P, Erbaykent-Tepedelen B, Gozen O and Erzurumlu Y: Divergent modulation of proteostasis in prostate cancer. *Adv Exp Med Biol* 1233: 117-151, 2020.
96. Park SH, Fong KW, Kim J, Wang F, Lu X, Lee Y, Brea LT, Wadosky K, Guo C, Abdulkadir SA, *et al*: Posttranslational regulation of FOXA1 by Polycomb and BUB3/USP7 deubiquitin complex in prostate cancer. *Sci Adv* 7: eabe2261, 2021.
97. Sun T, Lee GS, Oh WK, Pomerantz M, Yang M, Xie W, Freedman ML and Kantoff PW: Single-nucleotide polymorphisms in p53 pathway and aggressiveness of prostate cancer in a Caucasian population. *Clin Cancer Res* 16: 5244-5251, 2010.
98. Ren X, Jiang M, Ding P, Zhang X, Zhou X, Shen J, Liu D, Yan X and Ma Z: Ubiquitin-specific protease 28: The decipherment of its dual roles in cancer development. *Exp Hematol Oncol* 12: 27, 2023.
99. Chen L, Xu Z, Li Q, Zheng C, Du Y, Yuan R and Peng X: USP28 facilitates pancreatic cancer progression through activation of Wnt/ β -catenin pathway via stabilising FOXM1. *Cell Death Dis* 12: 887, 2021.
100. Zhao LJ, Zhang T, Feng XJ, Chang J, Suo FZ, Ma JL, Liu YJ, Liu Y, Zheng YC and Liu HM: USP28 contributes to the proliferation and metastasis of gastric cancer. *J Cell Biochem* 120: 7657-7666, 2019.
101. Wang H, Meng Q, Ding Y, Xiong M, Zhu M, Yang Y, Su H, Gu L, Xu Y, Shi L, *et al*: USP28 and USP25 are downregulated by Vismodegib in vitro and in colorectal cancer cell lines. *FEBS J* 288: 1325-1342, 2021.
102. Devrim T, Ataç F, Devrim AK and Balci M: The concomitant use of USP28 and p53 to predict the progression of urothelial carcinoma of the bladder. *Pathol Res Pract* 216: 152774, 2020.
103. Fong CS, Mazo G, Das T, Goodman J, Kim M, O'Rourke BP, Izquierdo D and Tsou MF: 53BP1 and USP28 mediate p53-dependent cell cycle arrest in response to centrosome loss and prolonged mitosis. *Elife* 5: e16270, 2016.
104. Tzavlaki K and Moustakas A: TGF- β Signaling. *Biomolecules* 10: 487, 2020.
105. Derynck R and Budi EH: Specificity, versatility, and control of TGF- β family signaling. *Sci Signal* 12: eaav5183, 2019.
106. Hata A and Chen YG: TGF- β Signaling from Receptors to Smads. *Cold Spring Harb Perspect Biol* 8: a022061, 2016.
107. Peng D, Fu M, Wang M, Wei Y and Wei X: Targeting TGF- β signal transduction for fibrosis and cancer therapy. *Mol Cancer* 21: 104, 2022.
108. Zhang Y, Alexander PB and Wang XF: TGF- β family signaling in the control of cell proliferation and survival. *Cold Spring Harb Perspect Biol* 9: a022145, 2017.
109. Haque S and Morris JC: Transforming growth factor- β : A therapeutic target for cancer. *Hum Vaccin Immunother* 13: 1741-1750, 2017.
110. Sakai K, Ito C, Wakabayashi M, Kanzaki S, Ito T, Takada S, Toshimori K, Sekita Y and Kimura T: Usp26 mutation in mice leads to defective spermatogenesis depending on genetic background. *Sci Rep* 9: 13757, 2019.
111. Tang J, Luo Y and Xiao L: USP26 promotes anaplastic thyroid cancer progression by stabilizing TAZ. *Cell Death Dis* 13: 326, 2022.
112. Ye Y, Li M, Pan Q, Fang X, Yang H, Dong B, Yang J, Zheng Y, Zhang R and Liao Z: Machine learning-based classification of deubiquitinase USP26 and its cell proliferation inhibition through stabilizing KLF6 in cervical cancer. *Comput Biol Med* 168: 107745, 2024.
113. Li G, Qi HW, Dong HG, Bai P, Sun M and Liu HY: Targeting deubiquitinating enzyme USP26 by microRNA-203 regulates Snail's pro-metastatic functions in esophageal cancer. *Cancer Cell Int* 20: 355, 2020.
114. Wosnitzer MS, Mielnik A, Dabaja A, Robinson B, Schlegel PN and Paduch DA: Ubiquitin Specific Protease 26 (USP26) expression analysis in human testicular and extragonadal tissues indicates diverse action of USP26 in cell differentiation and tumorigenesis. *PLoS One* 9: e98638, 2014.
115. Dirac AM and Bernards R: The deubiquitinating enzyme USP26 is a regulator of androgen receptor signaling. *Mol Cancer Res* 8: 844-854, 2010.
116. Cai Q, Chen Y, Zhang D, Pan J, Xie Z, Ma S, Liu C, Zuo J, Zhou X, Quan C, *et al*: Loss of epithelial AR increase castration resistant stem-like prostate cancer cells and promotes cancer metastasis via TGF- β 1/EMT pathway. *Transl Androl Urol* 9: 1013-1027, 2020.
117. Allen-Petersen BL and Sears RC: Mission Possible: Advances in MYC Therapeutic Targeting in Cancer. *BioDrugs* 33: 539-553, 2019.
118. Blackwood EM and Eisenman RN: Max: A helix-loop-helix zipper protein that forms a sequence-specific DNA-binding complex with Myc. *Science* 251: 1211-1217, 1991.
119. Blackwood EM, Lüscher B, Kretzner L and Eisenman RN: The Myc:Max protein complex and cell growth regulation. *Cold Spring Harb Symp Quant Biol* 56: 109-117, 1991.
120. Helander S, Montecchio M, Pilstål R, Su Y, Kuruvilla J, Elvén M, Ziauddin JME, Anandapadamanaban M, Cristobal S, Lundström P, *et al*: Pre-anchoring of Pin1 to unphosphorylated c-Myc in a fuzzy complex regulates c-Myc activity. *Structure* 23: 2267-2279, 2015.
121. Kato GJ, Barrett J, Villa-Garcia M and Dang CV: An amino-terminal c-myc domain required for neoplastic transformation activates transcription. *Mol Cell Biol* 10: 5914-5920, 1990.
122. Prendergast GC and Ziff EB: Methylation-sensitive sequence-specific DNA binding by the c-Myc basic region. *Science* 251: 186-189, 1991.
123. Ashrafizadeh M, Zarabi A, Hushmandi K, Moghadam ER, Hashemi F, Daneshi S, Hashemi F, Tavakol S, Mohammadnejad R, Najafi M, *et al*: C-Myc signaling pathway in treatment and prevention of brain tumors. *Curr Cancer Drug Targets* 21: 2-20, 2021.
124. Park JH, Pyun WY and Park HW: Cancer Metabolism: Phenotype, signaling and therapeutic targets. *Cells* 9: 2308, 2020.
125. Chen H, Liu H and Qing G: Targeting oncogenic Myc as a strategy for cancer treatment. *Signal Transduct Target Ther* 3: 5, 2018.

126. Yang S, Wang J, Guo S, Huang D, Lorigados IB, Nie X, Lou D, Li Y, Liu M, Kang Y, *et al*: Transcriptional activation of USP16 gene expression by NF κ B signaling. *Mol Brain* 12: 120, 2019.
127. Zheng J, Chen C, Guo C, Caba C, Tong Y and Wang H: The pleiotropic ubiquitin-specific peptidase 16 and its many substrates. *Cells* 12: 886, 2023.
128. Liu S, Li H, Zhu Y, Ma X, Shao Z, Yang Z, Cai C, Wu Z, Li M, Gong W and Wu X: LncRNA MNX1-AS1 sustains inactivation of Hippo pathway through a positive feedback loop with USP16/IGF2BP3 axis in gallbladder cancer. *Cancer Lett* 547: 215862, 2022.
129. Xu G, Yang Z, Ding Y, Liu Y, Zhang L, Wang B, Tang M, Jing T, Jiao K, Xu X, *et al*: The deubiquitinase USP16 functions as an oncogenic factor in K-RAS-driven lung tumorigenesis. *Oncogene* 40: 5482-5494, 2021.
130. Li Y, Rao Y, Zhu H, Jiang B and Zhu M: USP16 regulates the stability and function of LDL receptor by Deubiquitination. *Int Heart J* 61: 1034-1040, 2020.
131. Ge J, Yu W, Li J, Ma H, Wang P, Zhou Y, Wang Y, Zhang J and Shi G: USP16 regulates castration-resistant prostate cancer cell proliferation by deubiquitinating and stabilizing c-Myc. *J Exp Clin Cancer Res* 40: 59, 2021.
132. He L, Liu X, Yang J, Li W, Liu S, Liu X, Yang Z, Ren J, Wang Y, Shan L, *et al*: Imbalance of the reciprocally inhibitory loop between the ubiquitin-specific protease USP43 and EGFR/PI3K/AKT drives breast carcinogenesis. *Cell Res* 28: 934-951, 2018.
133. Ye DX, Wang SS, Huang Y, Wang XJ and Chi P: USP43 directly regulates ZEB1 protein, mediating proliferation and metastasis of colorectal cancer. *J Cancer* 12: 404-416, 2021.
134. Xue Y, Li M, Hu J, Song Y, Guo W, Miao C, Ge D, Hou Y, Wang X, Huang X, *et al*: Ca(v)2.2-NFAT2-USP43 axis promotes invadopodia formation and breast cancer metastasis through cortactin stabilization. *Cell Death Dis* 13: 812, 2022.
135. Sun Q, Zhang H, Zong L, Julaiti A, Jing X and Zhang L: Prognostic value and oncogenic effects of ubiquitin-specific protease 43 in lung squamous cell carcinoma. *Tohoku J Exp Med* 257: 135-145, 2022.
136. Zhao Z, Lin Z, Guo X, Al-Danakh A, He H, Qin H, Ma C, Zhang N and Tan G: Ubiquitin-specific protease 43 impacts pancreatic ductal adenocarcinoma prognosis by altering its proliferation and infiltration of surrounding immune cells. *J Immunol Res* 2023: 4311388, 2023.
137. Lavaud M, Mullard M, Tesfaye R, Amiaud J, Legrand M, Danieau G, Brion R, Morice S, Regnier L, Dupuy M, *et al*: Overexpression of the Ubiquitin Specific Proteases USP43, USP41, USP27x and USP6 in Osteosarcoma Cell Lines: Inhibition of Osteosarcoma Tumor Growth and Lung Metastasis Development by the USP Antagonist PR619. *Cells* 10: 2268, 2021.
138. Li M, Yu J, Ju L, Wang Y, Jin W, Zhang R, Xiang W, Ji M, Du W, Wang G, *et al*: USP43 stabilizes c-Myc to promote glycolysis and metastasis in bladder cancer. *Cell Death Dis* 15: 44, 2024.
139. Nusse R and Varmus HE: Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. *Cell* 31: 99-109, 1982.
140. Zou G and Park JI: Wnt signaling in liver regeneration, disease, and cancer. *Clin Mol Hepatol* 29: 33-50, 2023.
141. Clevers H and Nusse R: Wnt/ β -catenin signaling and disease. *Cell* 149: 1192-1205, 2012.
142. Steinhart Z and Angers S: Wnt signaling in development and tissue homeostasis. *Development* 145: dev146589, 2018.
143. Zhan T, Rindtorff N and Boutros M: Wnt signaling in cancer. *Oncogene* 36: 1461-1473, 2017.
144. Hafez N, Modather El-Awadly Z and Arafa RK: UCH-L3 structure and function: Insights about a promising drug target. *Eur J Med Chem* 227: 113970, 2022.
145. Zhu T, Xu L, Peng J, Chen M and Xu H: Molecular characteristics and immune function of ubiquitin C-terminal hydrolase-L3 in *Macrobrachium nipponense*. *Fish Shellfish Immunol* 121: 295-304, 2022.
146. Ma Q, Lu Q, Lei X, Zhao J, Sun W, Wang J, Zhu Q and Huang D: UCHL3 promotes hepatocellular carcinoma cell migration by de-ubiquitinating and stabilizing Vimentin. *Front Oncol* 13: 1088475, 2023.
147. Zhang Y, Liu JB, Liu J, Liu M, Liu HL and Zhang J: UCHL3 promotes cervical cancer development and metastasis by stabilizing NRF2 via deubiquitination. *Biochem Biophys Res Commun* 641: 132-138, 2023.
148. Li J, Zheng Y, Li X, Dong X, Chen W, Guan Z and Zhang C: UCHL3 promotes proliferation of colorectal cancer cells by regulating SOX12 via AKT/mTOR signaling pathway. *Am J Transl Res* 12: 6445-6454, 2020.
149. Moroney MR, Woodruff E, Qamar L, Bradford AP, Wolsky R, Bitler BG and Corr BR: Inhibiting Wnt/ β -catenin in CTNNB1-mutated endometrial cancer. *Mol Carcinog* 60: 511-523, 2021.
150. Liu T, Fan MQ, Xie XX, Shu QP, Du XH, Qi LZ, Zhang XD, Zhang MH, Shan G, Du RL and Li SZ: Activation of CTNNB1 by deubiquitinase UCHL3-mediated stabilization facilitates bladder cancer progression. *J Transl Med* 21: 656, 2023.
151. Zhou L, Qin B, Yassine DM, Luo M, Liu X, Wang F and Wang Y: Structure and function of the highly homologous deubiquitinases ubiquitin specific peptidase 25 and 28: Insights into their pathophysiological and therapeutic roles. *Biochem Pharmacol* 213: 115624, 2023.
152. Zhong B, Liu X, Wang X, Liu X, Li H, Darnay BG, Lin X, Sun SC and Dong C: Ubiquitin-specific protease 25 regulates TLR4-dependent innate immune responses through deubiquitination of the adaptor protein TRAF3. *Sci Signal* 6: ra35, 2013.
153. Liu B, Miao X, Shen J, Lou L, Chen K, Mei F, Chen M, Su X, Du X, Zhu Z, *et al*: USP25 ameliorates diabetic nephropathy by inhibiting TRAF6-mediated inflammatory responses. *Int Immunopharmacol* 124(Pt A): 110877, 2023.
154. Ye B, Zhou H, Chen Y, Luo W, Lin W, Zhao Y, Han J, Han X, Huang W, Wu G, *et al*: USP25 Ameliorates Pathological Cardiac Hypertrophy by Stabilizing SERCA2a in Cardiomyocytes. *Circ Res* 132: 465-480, 2023.
155. Zheng Q, Song B, Li G, Cai F, Wu M, Zhao Y, Jiang L, Guo T, Shen M, Hou H, *et al*: USP25 inhibition ameliorates Alzheimer's pathology through the regulation of APP processing and A β generation. *J Clin Invest* 132: e152170, 2022.
156. Cheng H, Li X, Wang C, Chen Y, Li S, Tan J, Tan B and He Y: Inhibition of tankyrase by a novel small molecule significantly attenuates prostate cancer cell proliferation. *Cancer Lett* 443: 80-90, 2019.
157. Gu Z, Lin C, Hu J, Xia J, Wei S and Gao D: USP34 Regulated Human Pancreatic Cancer Cell Survival via AKT and PKC Pathways. *Biol Pharm Bull* 42: 573-579, 2019.
158. Guo YC, Wang MY, Zhang SW, Wu YS, Zhou CC, Zheng RX, Shao B, Wang Y, Xie L, Liu WQ, *et al*: Ubiquitin-specific protease USP34 controls osteogenic differentiation and bone formation by regulating BMP2 signaling. *EMBO J* 37: e99398, 2018.
159. Zhu Q, Liang P, Meng H, Li F, Miao W, Chu C, Wang W, Li D, Chen C, Shi Y, *et al*: Stabilization of Pin1 by USP34 promotes Ubc9 isomerization and protein sumoylation in glioma stem cells. *Nat Commun* 15: 40, 2024.
160. Lui TT, Lacroix C, Ahmed SM, Goldenberg SJ, Leach CA, Daulat AM and Angers S: The ubiquitin-specific protease USP34 regulates axin stability and Wnt/ β -catenin signaling. *Mol Cell Biol* 31: 2053-2065, 2011.
161. Zhao Y, Yan Y, Ma R, Lv X, Zhang L, Wang J, Zhu W, Zhao L, Jiang L, Zhao L, *et al*: Expression signature of six-snoRNA serves as novel non-invasive biomarker for diagnosis and prognosis prediction of renal clear cell carcinoma. *J Cell Mol Med* 24: 2215-2228, 2020.
162. Ma S, Meng Z, Chen R and Guan KL: The Hippo Pathway: Biology and Pathophysiology. *Annu Rev Biochem* 88: 577-604, 2019.
163. Lee U, Cho EY and Jho EH: Regulation of Hippo signaling by metabolic pathways in cancer. *Biochim Biophys Acta Mol Cell Res* 1869: 119201, 2022.
164. Wu Z and Guan KL: Hippo Signaling in Embryogenesis and Development. *Trends Biochem Sci* 46: 51-63, 2021.
165. Cao Z, An L, Han Y, Jiao S and Zhou Z: The Hippo signaling pathway in gastric cancer. *Acta Biochim Biophys Sin (Shanghai)* 55: 893-903, 2023.
166. Zhu N, Yang R, Wang X, Yuan L, Li X, Wei F and Zhang L: The Hippo signaling pathway: From multiple signals to the hallmarks of cancers. *Acta Biochim Biophys Sin (Shanghai)* 55: 904-913, 2023.
167. Gu Y, Wu S, Fan J, Meng Z, Gao G, Liu T, Wang Q, Xia H, Wang X and Wu K: CYLD regulates cell ferroptosis through Hippo/YAP signaling in prostate cancer progression. *Cell Death Dis* 15: 79, 2024.
168. Abdul Rehman SA, Kristariyanto YA, Choi SY, Nkosi PJ, Weidlich S, Labib K, Hofmann K and Kulathu Y: MINDY-1 is a member of an evolutionarily conserved and structurally distinct new family of deubiquitinating enzymes. *Mol Cell* 63: 146-155, 2016.

169. Tang J, Luo Y, Long G and Zhou L: MINDY1 promotes breast cancer cell proliferation by stabilizing estrogen receptor α . *Cell Death Dis* 12: 937, 2021.
170. Xia BL, Liu KW, Huang HX, Shen MM, Wang B and Gao J: Deubiquitinating enzyme MINDY1 is an independent risk factor for the maintenance of stemness and poor prognosis in liver cancer cells. *Zhonghua Gan Zang Bing Za Zhi* 31: 518-523, 2023 (In Chinese).
171. James C, Zhao TY, Rahim A, Saxena P, Muthalif NA, Uemura T, Tsuneyoshi N, Ong S, Igarashi K, Lim CY, *et al*: MINDY1 Is a Downstream Target of the Polyamines and Promotes Embryonic Stem Cell Self-Renewal. *Stem Cells* 36: 1170-1178, 2018.
172. Luo Y, Zhou J, Tang J, Zhou F, He Z, Liu T and Liu T: MINDY1 promotes bladder cancer progression by stabilizing YAP. *Cancer Cell Int* 21: 395, 2021.
173. Dai C, Heemers H and Sharifi N: Androgen signaling in prostate cancer. *Cold Spring Harb Perspect Med* 7: a030452, 2017.
174. Deng CC, Zhu DH, Chen YJ, Huang TY, Peng Y, Liu SY, Lu P, Xue YH, Xu YP, Yang B and Rong Z: TRAF4 Promotes Fibroblast Proliferation in Keloids by Destabilizing p53 via Interacting with the Deubiquitinase USP10. *J Invest Dermatol* 139: 1925-1935.e5, 2019.
175. Zeng Z, Wu HX, Zhan N, Huang YB, Wang ZS, Yang GF, Wang P and Fu GH: Prognostic significance of USP10 as a tumor-associated marker in gastric carcinoma. *Tumour Biol* 35: 3845-3853, 2014.
176. Lu C, Ning Z, Wang A, Chen D, Liu X, Xia T, Tekcham DS, Wang W, Li T, Liu X, *et al*: USP10 suppresses tumor progression by inhibiting mTOR activation in hepatocellular carcinoma. *Cancer Lett* 436: 139-148, 2018.
177. Ye Z, Chen J, Huang P, Xuan Z and Zheng S: Ubiquitin-specific peptidase 10, a deubiquitinating enzyme: Assessing its role in tumor prognosis and immune response. *Front Oncol* 12: 990195, 2022.
178. Kong L and Jin X: Dysregulation of deubiquitination in breast cancer. *Gene* 902: 148175, 2024.
179. An T, Lu Y, Yan X and Hou J: Insights Into the Properties, Biological Functions, and Regulation of USP21. *Front Pharmacol* 13: 944089, 2022.
180. Chen Y, Wang L, Jin J, Luan Y, Chen C, Li Y, Chu H, Wang X, Liao G, Yu Y, *et al*: p38 inhibition provides anti-DNA virus immunity by regulation of USP21 phosphorylation and STING activation. *J Exp Med* 214: 991-1010, 2017.
181. Liu J, Kruswick A, Dang H, Tran AD, Kwon SM, Wang XW and Oberdoerffer P: Ubiquitin-specific protease 21 stabilizes BRCA2 to control DNA repair and tumor growth. *Nat Commun* 8: 137, 2017.
182. Chen Y, Zhou B and Chen D: USP21 promotes cell proliferation and metastasis through suppressing EZH2 ubiquitination in bladder carcinoma. *Onco Targets Ther* 10: 681-689, 2017.
183. Lin Z, Yang H, Kong Q, Li J, Lee SM, Gao B, Dong H, Wei J, Song J, Zhang DD and Fang D: USP22 antagonizes p53 transcriptional activation by deubiquitinating Sirt1 to suppress cell apoptosis and is required for mouse embryonic development. *Mol Cell* 46: 484-494, 2012.
184. Feng T, Ling S, Xu C, Ying L, Su D and Xu X: Ubiquitin-specific peptidase 22 in cancer. *Cancer Lett* 514: 30-37, 2021.
185. Zeng K, Xie W, Wang C, Wang S, Liu W, Su Y, Lin L, Zou R, Sun G, Zhou B, *et al*: USP22 upregulates ZEB1-mediated VEGFA transcription in hepatocellular carcinoma. *Cell Death Dis* 14: 194, 2023.
186. Xu G, Cai J, Wang L, Jiang L, Huang J, Hu R and Ding F: MicroRNA-30e-5p suppresses non-small cell lung cancer tumorigenesis by regulating USP22-mediated Sirt1/JAK/STAT3 signaling. *Exp Cell Res* 362: 268-278, 2018.
187. Yuan X, Wang H, Xu A, Zhu X, Zhan Y and Wang W: Ubiquitin-specific peptidase 22 promotes proliferation and metastasis in human colon cancer. *Oncol Lett* 18: 5567-5576, 2019.
188. Lv L, Xiao XY, Gu ZH, Zeng FQ, Huang LQ and Jiang GS: Silencing USP22 by asymmetric structure of interfering RNA inhibits proliferation and induces cell cycle arrest in bladder cancer cells. *Mol Cell Biochem* 346: 11-21, 2011.
189. Guo J, Zhao J, Fu W, Xu Q and Huang D: Immune Evasion and Drug Resistance Mediated by USP22 in Cancer: Novel Targets and Mechanisms. *Front Immunol* 13: 918314, 2022.
190. Nag N and Dutta S: Deubiquitination in prostate cancer progression: Role of USP22. *J Cancer Metastasis Treat* 6: 16, 2020.
191. Li C, Zeng X, Qiu S, Gu Y and Zhang Y: Nanomedicine for urologic cancers: Diagnosis and management. *Semin Cancer Biol* 86: 463-475, 2022.
192. Schauer NJ, Magin RS, Liu X, Doherty LM and Buhlrlage SJ: Advances in Discovering Deubiquitinating Enzyme (DUB) Inhibitors. *J Med Chem* 63: 2731-2750, 2020.
193. Lee JE, Park CM and Kim JH: USP7 deubiquitinates and stabilizes EZH2 in prostate cancer cells. *Genet Mol Biol* 43: e20190338, 2020.
194. Zhang W, Zhang J, Xu C, Zhang S, Bian S, Jiang F, Ni W, Qu L, Lu C, Ni R, *et al*: Ubiquitin-specific protease 7 is a drug-able target that promotes hepatocellular carcinoma and chemoresistance. *Cancer Cell Int* 20: 28, 2020.
195. Chen H, Zhu X, Sun R, Ma P, Zhang E, Wang Z, Fan Y, Zhou G and Mao R: Ubiquitin-specific protease 7 is a druggable target that is essential for pancreatic cancer growth and chemoresistance. *Invest New Drugs* 38: 1707-1716, 2020.
196. Wang S, Kollipara RK, Srivastava N, Li R, Ravindranathan P, Hernandez E, Freeman E, Humphries CG, Kapur P, Lotan Y, *et al*: Ablation of the oncogenic transcription factor ERG by deubiquitinase inhibition in prostate cancer. *Proc Natl Acad Sci USA* 111: 4251-4256, 2014.
197. Stolte B, Iniguez AB, Dharra NV, Robichaud AL, Conway AS, Morgan AM, Alexe G, Schauer NJ, Liu X, Bird GH, *et al*: Genome-scale CRISPR-Cas9 screen identifies druggable dependencies in TP53 wild-type Ewing sarcoma. *J Exp Med* 215: 2137-2155, 2018.
198. Turnbull AP, Ioannidis S, Krajewski WW, Pinto-Fernandez A, Heride C, Martin ACL, Tonkin LM, Townsend EC, Buker SM, Lancia DR, *et al*: Molecular basis of USP7 inhibition by selective small-molecule inhibitors. *Nature* 550: 481-486, 2017.
199. Xu S, Adisetiyo H, Tamura S, Grande F, Garofalo A, Roy-Burman P and Neamati N: Dual inhibition of survivin and MAOA synergistically impairs growth of PTEN-negative prostate cancer. *Br J Cancer* 113: 242-251, 2015.
200. Tolcher AW, Quinn DI, Ferrari A, Ahmann F, Giaccone G, Drake T, Keating A and de Bono JS: A phase II study of YM155, a novel small-molecule suppressor of survivin, in castration-resistant taxane-pretreated prostate cancer. *Ann Oncol* 23: 968-973, 2012.
201. Chow PM, Dong JR, Chang YW, Kuo KL, Lin WC, Liu SH and Huang KH: The UCHL5 inhibitor b-API5 overcomes cisplatin resistance via suppression of cancer stemness in urothelial carcinoma. *Mol Ther Oncolytics* 26: 387-398, 2022.
202. Jamroze A, Chatta G and Tang DG: Androgen receptor (AR) heterogeneity in prostate cancer and therapy resistance. *Cancer Lett* 518: 1-9, 2021.
203. He Y, Xu W, Xiao YT, Huang H, Gu D and Ren S: Targeting signaling pathways in prostate cancer: mechanisms and clinical trials. *Signal Transduct Target Ther* 7: 198, 2022.
204. Schellhammer PF and Davis JW: An evaluation of bicalutamide in the treatment of prostate cancer. *Clin Prostate Cancer* 2: 213-219, 2004.
205. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto A, Merseburger AS, Özgüroğlu M, Uemura H, *et al*: Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 381: 13-24, 2019.
206. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, Alcaraz A, Alekseev B, Iguchi T, Shore ND, *et al*: ARCHES: A Randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 37: 2974-2986, 2019.
207. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, *et al*: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 377: 352-360, 2017.
208. Isaacsson Velho P and Antonarakis ES: PD-1/PD-L1 pathway inhibitors in advanced prostate cancer. *Expert Rev Clin Pharmacol* 11: 475-486, 2018.
209. Wu X, Gu Z, Chen Y, Chen B, Chen W, Weng L and Liu X: Application of PD-1 Blockade in Cancer Immunotherapy. *Comput Struct Biotechnol J* 17: 661-674, 2019.
210. Kuang Z, Liu X, Zhang N, Dong J, Sun C, Yin M, Wang Y, Liu L, Xiao D, Zhou X, *et al*: USP2 promotes tumor immune evasion via deubiquitination and stabilization of PD-L1. *Cell Death Differ* 30: 2249-2264, 2023.

211. Sweeney PL, Suri Y, Basu A, Koshkin VS and Desai A: Mechanisms of tyrosine kinase inhibitor resistance in renal cell carcinoma. *Cancer Drug Resist* 6: 858-873, 2023.
212. Ebrahimi N, Fardi E, Ghaderi H, Palizdar S, Khorram R, Vafadar R, Ghanaatian M, Rezaei-Tazangi F, Baziyar P, Ahmadi A, *et al*: Receptor tyrosine kinase inhibitors in cancer. *Cell Mol Life Sci* 80: 104, 2023.
213. McCann AP, Smyth P, Cogo F, McDaid WJ, Jiang L, Lin J, Evergren E, Burden RE, Van Schaeybroeck S, Scott CJ and Burrows JF: USP17 is required for trafficking and oncogenic signaling of mutant EGFR in NSCLC cells. *Cell Commun Signal* 16: 77, 2018.
214. Popova NV and Jücker M: The Role of mTOR signaling as a therapeutic target in cancer. *Int J Mol Sci* 22: 1743, 2021.
215. Hasskarl J: Everolimus. *Recent Results Cancer Res* 211: 101-123, 2018.
216. Stock C, Zaccagnini M, Schulze M, Teber D and Rassweiler JJ: Temsirolimus. *Recent Results Cancer Res* 184: 189-197, 2010.
217. Porta C, Calvo E, Climent MA, Vaishampayan U, Osanto S, Ravaud A, Bracarda S, Hutson TE, Escudier B, Grünwald V, *et al*: Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 Trial. *Eur Urol* 61: 826-833, 2012.
218. Roldán-Romero JM, Valdivia C, Santos M, Lanillos J, Maroto P, Anguera G, Calsina B, Martinez-Montes A, Monteagudo M, Mellid S, *et al*: Deubiquitinase USP9X loss sensitizes renal cancer cells to mTOR inhibition. *Int J Cancer* 153: 1300-1312, 2023.



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