Deubiquitinating enzymes in kidney diseases: Molecular mechanisms, pathological roles and therapeutic opportunities (Review)

QIANQIAN LI*, YUFANG NI*, ZHAOYANG LI, JIANCHUN LI and LI WANG

Research Center of Integrated Traditional Chinese and Western Medicine, The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, Luzhou, Sichuan 646000, P.R. China

Received May 12, 2026; Accepted July 27, 2026

DOI: 10.3892/mmr.2026.13994

Abstract. The ubiquitin-proteasome system maintains cellular protein turnover and quality control through the coordinated action of ubiquitin ligases and deubiquitinating enzymes (DUBs). While the functions of E3 ubiquitin ligases have been extensively investigated in renal disease, the ~100 human DUBs distributed across seven structurally distinct families have recently emerged as important regulators of renal physiology and pathology. The present review organizes current knowledge of DUB-mediated regulation in kidney disease around functional themes rather than individual disease categories. The present review discusses how DUBs regulate inflammatory signaling, TGF-β-mediated fibrotic responses, epithelial-to-mesenchymal transition (EMT), mitochondrial homeostasis, multiple forms of programmed cell death, podocyte homeostasis, and oncogenic pathways in renal cell carcinoma. Several DUBs, including A20 (TNFAIP3), CYLD, USP25 and OTUD5, restrain inflammation and fibrosis, whereas USP11, OTUD1, and USP22 promote disease progression through substrate stabilization. The translational landscape of DUB inhibitors, PROTAC degraders, and the DUBTAC platform for targeted protein stabilization, along with the selectivity and delivery challenges that remain, were discussed. Key unanswered questions, including cell-type-specific DUB functions, ubiquitin chain linkage context, and the therapeutic window for DUB modulation in the kidney, are outlined as priorities for future investigation.

Correspondence to: Professor Jianchun Li or Professor Li Wang, Research Center of Integrated Traditional Chinese and Western Medicine, The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, 182 Chunhui Road, Longmatan, Luzhou, Sichuan 646000, P.R. China
E-mail: lijianchunchina@swmu.edu.cn
E-mail: wangli111@swmu.edu.cn

*Contributed equally

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; ccRCC, clear cell RCC; CKD, chronic kidney disease; DKD, diabetic kidney disease; DUB, deubiquitinating enzyme; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ESRD, end-stage renal disease; HIF, hypoxia-inducible factor; I/R, ischemia-reperfusion; LN, lupus nephritis; MINDY, motif interacting with Ub-containing novel DUB family; MJD, Machado-Joseph disease proteases; NF-κB, nuclear factor κB; OTU, ovarian tumor protease; PROTAC, proteolysis-targeting chimera; RCC, renal cell carcinoma; RTEC, renal tubular epithelial cell; SASP, senescence-associated secretory phenotype; TGF-β, transforming growth factor β; TLR, Toll-like receptor; UPS, ubiquitin-proteasome system; USP, ubiquitin-specific protease; UUO, unilateral ureteral obstruction; VHL, von Hippel-Lindau

Key words: DUB, kidney disease, renal fibrosis, UPS, AKI, DKD, RCC

Contents

1. Introduction

Kidney disorders impose a substantial global health burden, affecting over 10% of the global population (1). Regardless of etiology, chronic kidney disease (CKD) converges on renal fibrosis and progressive nephron loss (2-4). Acute kidney injury (AKI) induced by ischemia-reperfusion injury, septic insults, or nephrotoxins is now recognized as an important driver

of CKD progression rather than a self-limiting event (5-8). Diabetic kidney disease (DKD) is the predominant cause of end-stage renal disease (ESRD) worldwide (9,10). Renal cell carcinoma (RCC), polycystic kidney disease and immune-mediated glomerular diseases add further layers of complexity to the renal disease spectrum (11). A shared set of signaling pathways, TGF-β/SMAD, NF-κB, Wnt/β-catenin and hypoxia-inducible factor (HIF), coordinates injury, inflammation and fibrosis across these conditions (12-18).

Ubiquitination is a reversible post-translational modification that, similar to phosphorylation, controls protein stability, localization and signal transduction through the conjugation of ubiquitin onto substrate lysine residues (19). This reversible modification is maintained by the opposing activities of ubiquitin ligases (E3s) and deubiquitinating enzymes (DUBs), thereby establishing a dynamic regulatory system. Studies of renal E3 ligases have yielded landmark discoveries, including the von Hippel-Lindau (VHL) tumor suppressor as a regulator of HIF stability (20). By comparison, the DUBs that counteract these ligases, thereby controlling whether a protein is degraded or preserved, have only recently drawn systematic attention.

A total of ~100 DUBs have been identified in the human genome and are classified into seven families: Ubiquitin-specific proteases (USPs, ~56 members), ubiquitin C-terminal hydrolases (UCHs, 4 members), ovarian tumor proteases (OTUs, ~16 members), Machado-Joseph disease proteases (MJDs, 4 members), the MINDY family (5 members), JAB1/MPN/MOV34 metalloproteases (JAMMs, ~14 members) and zinc finger ubiquitin peptidase 1 (ZUP1) (21,22). These enzymes differ in their catalytic mechanisms, ubiquitin chain linkage preferences, substrate recognition and domain architecture, all of which have important implications for the development of selective therapeutic strategies (23-25).

Accumulating evidence has begun to define the roles of DUBs in renal tubular epithelial cells, podocytes, mesangial cells and renal carcinomas. A consistent observation has emerged: Individual DUBs do not act as generic regulators of protein stability, but as relatively narrow, substrate-defined nodes that control specific pathological processes (26). The present review organizes these findings around shared functional themes inflammatory signaling, TGF-β-driven fibrosis and EMT, mitochondrial quality control and cell death, podocyte biology, and oncogenic signaling rather than presenting them disease by disease. The translational landscape was discussed and questions that must be addressed before DUB biology can be applied clinically in nephrology were identified.

2. Overview of the deubiquitinase families

Ubiquitination generates chains of varying topology: K48-linked polyubiquitin chains typically target proteins for proteasomal degradation, whereas K63-linked polyubiquitin chains primarily regulate protein interactions and signal transduction, and linear M1-linked chains predominantly regulate NF-κB signaling (27). DUBs edit this ubiquitin code by removing ubiquitin from conjugated substrates, an activity that can rescue proteins from degradation, alter their localization, modulate their activity, or terminate ubiquitin-dependent signaling (28-30).

The USP family, the largest, contains a papain-like cysteine-protease fold with a catalytic triad (Cys-His-Asp/Asn). A notable structural feature is allosteric activation upon ubiquitin binding: The catalytic residues, often misaligned in the resting state, achieve competence only when ubiquitin occupies the active site (31,32). Several USPs have emerged as kidney disease regulators. For instance, within the USP family, USP11 promotes pyroptosis by stabilizing KLF4 (33), whereas USP25 suppresses fibrosis by deubiquitinating SMAD4 and TRAF6 (34,35). This stark functional divergence highlights that a DUB's functional effect is dictated by its specific substrate and cellular context, not merely by its structural family.

Although smaller in number and often more restricted in substrate access than the USP family, the UCH, OTU and MJD families exert profound and distinct effects on renal pathology ranging from oncogenesis to fibrogenesis. The UCH family (UCHL1, UCHL3, UCHL5 and BAP1) contains a narrow active-site cleft that restricts substrate access (36). BAP1, a tumor suppressor mutated in a subset of RCC, functions as the catalytic subunit of a Polycomb repressive deubiquitinase (PR-DUB) complex responsible for removing ubiquitin from histone H2A (37). UCHL5, which associates with the 26S proteasome, has also been reported to cooperate with USP14 in renal fibrosis by promoting the bAP-15-sensitive p300 stabilization pathway (38). The OTU family shows strong ubiquitin chain linkage preferences: OTUD1, OTUD2 and OTUD5 preferentially cleave K63-linked chains, while OTUB1 is specific for K48 linkages (39,40). OTU DUBs have rapidly gained prominence in kidney research, with OTUD1 driving hypertensive fibrosis through CDK9 deubiquitination (41) and OTUD5 protecting podocytes through TAK1 deubiquitination (42). The MJD family (ATXN3, ATXN3L, JOSD1 and JOSD2) was not linked to kidney disease until a 2025 report showing that JOSD2 deubiquitinates SIRT7 to suppress NF-κB-driven inflammation in AKI (43). The MINDY, JAMM and ZUP1 families have not been studied in kidney tissue, representing knowledge gaps (44-46). Thus, despite their restricted substrate access or fewer members, these smaller DUB families exert profound and distinct effects on renal pathology.

3. DUBs as regulators of inflammatory signaling in kidney disease

Sterile inflammation, driven largely by NF-κB signaling, is a common feature of AKI, CKD and DKD. Several DUBs influence the amplitude and duration of NF-κB activation by editing the ubiquitination status of upstream signaling adaptors, receptor complexes, and the NF-κB subunits themselves. These DUBs can be grouped into those that restrain inflammation and those that amplify it (47-50).

DUBs that restrain renal inflammation. A20 (TNFAIP3) is a unique ubiquitin-editing enzyme that possesses both deubiquitinase and E3 ligase activities, thereby acting as a key negative regulator of NF-κB (51). Its relevance to kidney disease is supported by convergent genetic and functional evidence. Hypomorphic human *TNFAIP3* coding variants that impair A20 function are associated with altered AKI outcomes (52).

Mice with podocyte-specific deletion of A20 develop spontaneous glomerular injury, accompanied by loss of podocytes, foot process effacement and inflammatory infiltration (53). A recent study showed that A20 competitively binds NEK7 at Lys140, disrupting the NEK7-NLRP3 interaction required for inflammasome assembly, and that an A20-derived peptide was sufficient to alleviate AKI (54). These findings position A20 as a broad-spectrum suppressor of both NF-κB and inflammasome signaling in the kidney.

CYLD, a K63-specific deubiquitinase with tumor suppressor function, attenuates NF-κB signaling by removing K63-linked ubiquitin chains from TRAF2, TRAF6 and NEMO (55). Studies in human proximal tubular epithelial cells have shown that CYLD knockdown increases CCL5 production induced by poly I:C, together with enhanced IKK/NF-κB phosphorylation downstream of TLR3, identifying CYLD as a constitutive brake on antiviral innate immune signaling in the tubular compartment (56).

The protective function of USP25 extends beyond the TGF-β pathway (Section 4) to include suppression of inflammatory signaling in DKD. In streptozotocin-induced diabetic mice, USP25 localizes to both mesangial cells and infiltrating renal macrophages, where it suppresses TRAF6 signaling by cleaving K63-linked ubiquitin chains, attenuating AGE-induced NF-κB and MAPK activation (35). *USP25* knockout did not affect glycemic control but significantly worsened renal dysfunction and fibrosis, consistent with a specific anti-inflammatory role. USP25 therefore exemplifies a DUB that damps inflammation at two independent signaling nodes (TRAF6 in the NF-κB pathway and SMAD4 in the TGF-β pathway) through a shared K63-deubiquitination mechanism.

Additional DUBs with anti-inflammatory roles have been identified in sepsis-associated AKI. BAP1, a UCH family DUB, was shown to suppress NF-κB activation, thereby alleviating AKI in a murine model of sepsis, with this protection linked in part to stabilization of the BRCA1 protein (57). PRDM16 was reported to upregulate USP10, which suppresses pyroptosis in rhabdomyolysis-induced AKI (58), though the detailed mechanism awaits further characterization.

DUBs that amplify renal inflammation. In contrast to the aforementioned protective functions, several DUBs promote renal inflammation by stabilizing pro-inflammatory signaling components. OTUD1, an OTU family DUB, is upregulated in kidneys of Angiotensin II-infused mice. OTUD1 catalyzes K63 deubiquitination of CDK9 at Cys320, promoting CDK9 phosphorylation and activation to drive transcriptional elongation of inflammatory and pro-fibrotic genes. *Otud1* knockout mice are protected from hypertensive renal disease (41); the CDK9 inhibitor NVP-2 ameliorated the phenotype, confirming that OTUD1 acts through a CDK9-dependent mechanism.

USP9x contributes to sepsis-associated AKI by physically interacting with TLR4 and removing ubiquitin to prevent its degradation, thereby amplifying TLR4/NF-κB signaling in tubular epithelial cells. *USP9x* knockdown attenuated renal injury in rats subjected to cecal ligation and puncture, thereby mitigating AKI (59). USP10, despite its protective role in some AKI contexts, has also been reported to promote Angiotensin II-induced renal fibrosis by deubiquitinating and stabilizing TLR4, enhancing TLR4-mediated inflammatory signaling (60). These context-dependent observations suggest that the net effect of USP10 on renal inflammation depends on which substrate predominates under specific disease conditions.

Most conclusions regarding inflammatory DUBs derive from single knockout mouse models studied by individual laboratories. Independent replication in additional models and analysis of human kidney tissue would help establish the generalizability of these findings. The relative contribution of each DUB to the overall NF-κB response *in vivo*, and whether DUBs cooperate or compete at shared signaling nodes, has not been systematically addressed (Fig. 1).

4. DUBs at the TGF-β/EMT/fibrosis interface

Renal fibrosis is a hallmark of CKD progression and arises largely from persistent activation of TGF-β/SMAD signaling and the differentiation of fibroblasts into matrix-producing myofibroblasts. Tubular epithelial cells contribute to this process through partial EMT, senescence-associated secretory phenotype (SASP), and regulated cell death modalities including pyroptosis (19,61). DUBs influence renal fibrosis at multiple levels: By controlling the stability of TGF-β receptors and downstream SMAD proteins, by regulating EMT transcription factors, and by governing cell death pathways that trigger secondary inflammation and fibroblast activation (62-65).

USP11: A multi-substrate pro-fibrotic hub. USP11 is one of the most extensively validated pro-fibrotic DUBs in the kidney, with independent studies implicating it in renal fibrosis through at least three distinct substrates. It is consistently upregulated in fibrotic kidneys across CKD patient samples, UUO and Angiotensin II models (33,66,67).

The first characterized mechanism involves TGF-β type II receptor (TGFBR2): USP11 deubiquitinates and stabilizes TGFBR2, sensitizing tubular cells to TGF-β stimulation (67). A second mechanism was identified through which USP11 stabilizes the epidermal growth factor receptor (EGFR), augmenting TGF-β1 signaling and promoting an incomplete EMT accompanied by the simultaneous expression of epithelial and mesenchymal markers together with G2/M-phase arrest and increased secretion of profibrotic mediators (66). The third and most mechanistically detailed axis involves USP11-mediated stabilization of the transcription factor KLF4. KLF4 binds the promoter regions of Caspase-1 and Caspase-3, thereby enhancing their transcription and activating both the Caspase-1/GSDMD- and Caspase-3/GSDME-dependent pyroptotic programs in tubular epithelial cells (33). Consistently, tubular epithelial cell-specific deletion of *Klf4* or *Usp11* markedly attenuated pyroptotic injury and renal fibrosis in the UUO model. Pharmacological inhibition of USP11 with mitoxantrone (3 mg/kg twice weekly) reduced KLF4 levels, pyroptosis markers and ECM deposition, providing proof-of-concept for USP11 as a drug target in renal fibrosis.

The convergence of three structurally unrelated substrates, a receptor (TGFBR2), a growth factor receptor (EGFR), and a transcription factor (KLF4), under the regulation of a single DUB suggests that USP11 functions as a central pro-fibrotic regulator. These findings come primarily from the UUO and Angiotensin II models and from a single research consortium;

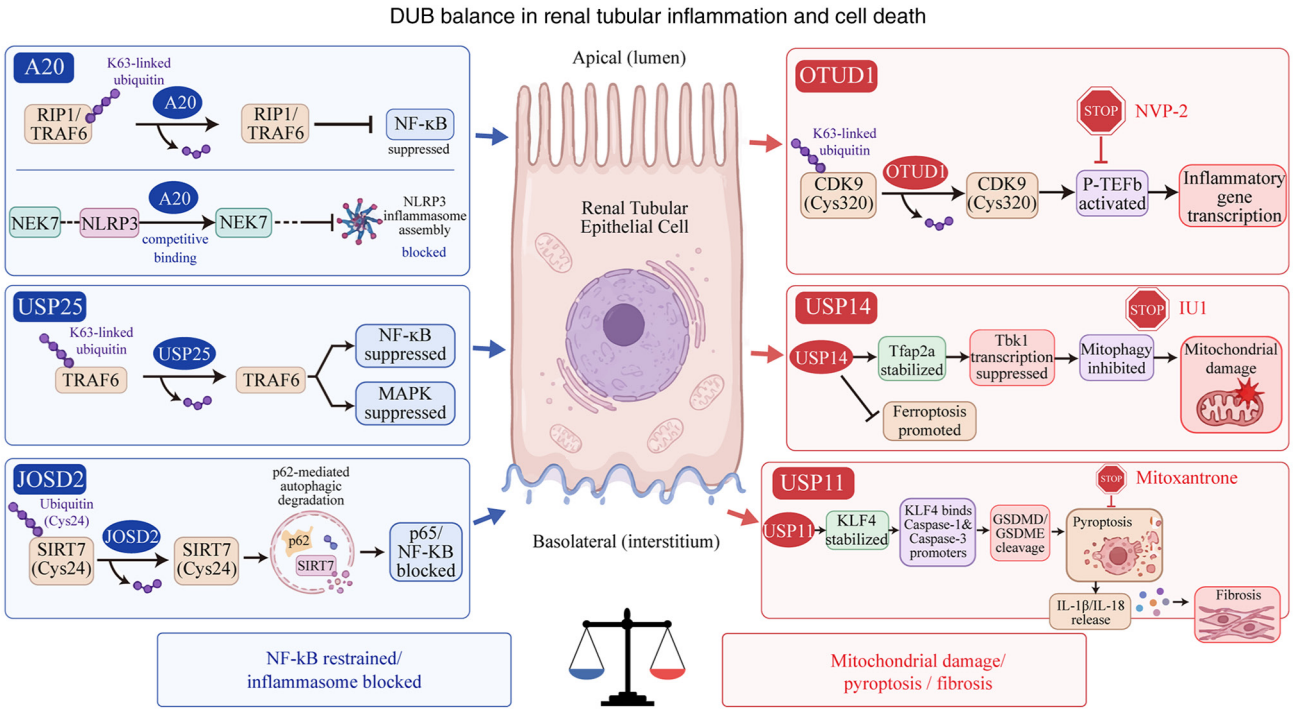

Figure 1. The DUB balance in renal tubular inflammation and cell death. Central renal tubular epithelial cell with six representative DUB-substrate pairs arranged as three left-right rows. Left (blue, protective): A20 removes K63-linked ubiquitin from RIP1/TRAF6 to suppress NF-κB and competitively binds NEK7 to block NLRP3 inflammasome assembly; USP25 removes K63 chains from TRAF6 to attenuate NF-κB and MAPK; JOSD2 deubiquitinates SIRT7 at Cys24, promoting its autophagic degradation to block p65/NF-κB. Right (red, pathogenic): OTUD1 deubiquitinates CDK9 at Cys320 to activate P-TEFb-driven inflammatory transcription; USP14 stabilizes Tfap2a to suppress mitophagy and promotes ferroptosis; USP11 stabilizes KLF4 to drive Caspase-1/GSDMD and Caspase-3/GSDME pyroptosis. Pharmacological interventions (NVP-2, IU1, mitoxantrone) are indicated where applicable. DUB, deubiquitinating enzyme; OTU, ovarian tumor protease.

independent replication in human tissue would help confirm USP11 as a clinical target.

DUBs that oppose fibrosis. USP25 inhibits fibrosis by removing K63-linked polyubiquitin from SMAD4, suppressing SMAD2 nuclear translocation and TGF-β-dependent transcription of pro-fibrotic genes (34). In Angiotensin II-induced hypertensive renal disease, *Usp25* knockout mice developed markedly worse fibrosis, whereas AAV9-mediated USP25 overexpression was protective. USP25 thus acts at a different node of the TGF-β pathway from USP11: While USP11 stabilizes the upstream receptor, USP25 suppresses the downstream transcriptional effector. A separate study identified OTUD7B as a protective OTU family DUB that attenuates fibrosis by deubiquitinating and stabilizing peroxiredoxin 1 (PRDX1), an antioxidant enzyme that limits oxidative stress-induced tubular injury (68).

DUBs that promote EMT and fibroblast activation. Several DUBs drive fibrosis by stabilizing EMT transcription factors or fibroblast-activating signals. USP22 deubiquitinates and stabilizes Snail1, a master regulator of EMT, in the renal tubular epithelium of diabetic db/db mice; silencing *Usp22* improved renal function and histology (69). USP36 maintains DOCK4 protein stability, thereby enhancing Wnt/β-catenin signaling and EMT in diabetic tubular cells (70). USP4 was found to deubiquitinate and stabilize the TGF-β type I receptor (TbRI); the flavonoid isovitexin inhibited USP4 and attenuated renal interstitial fibrosis (71). These studies identify USP22, USP36 and USP4 as potential targets for anti-fibrotic therapy, although the extent to which their pro-fibrotic functions are redundant or additive *in vivo* has not been determined. However, current evidence is derived predominantly from diabetic and experimental fibrosis models, and further validation in independent models and human kidney tissues will be necessary to establish the translational relevance of these findings.

USP14 and UCHL5: Proteasome-associated DUBs in fibrosis. USP14 and UCHL5, two DUBs associated with the 26S proteasome, were found to be consistently increased in kidney specimens from patients with CKD as well as in the UUO mouse model (38). The dual USP14/UCHL5 inhibitor bAP-15 reduced the stability of p300, a histone acetyltransferase and transcriptional co-activator that promotes pro-fibrotic gene expression. bAP-15 treatment suppressed the expression of EMT-associated proteins induced by TGF-β in tubular epithelial cells. It remains unclear whether the anti-fibrotic activity of bAP-15 primarily results from USP14 or UCHL5 inhibition, and whether the p300 stabilization mechanism operates independently of their proteasome-associated activities. The convergence of these DUBs at distinct levels of the TGF-β signaling cascade is illustrated in Fig. 2.

5. DUBs governing mitochondrial quality control and regulated cell death

Disruption of mitochondrial homeostasis, together with multiple forms of regulated cell death, including apoptosis,

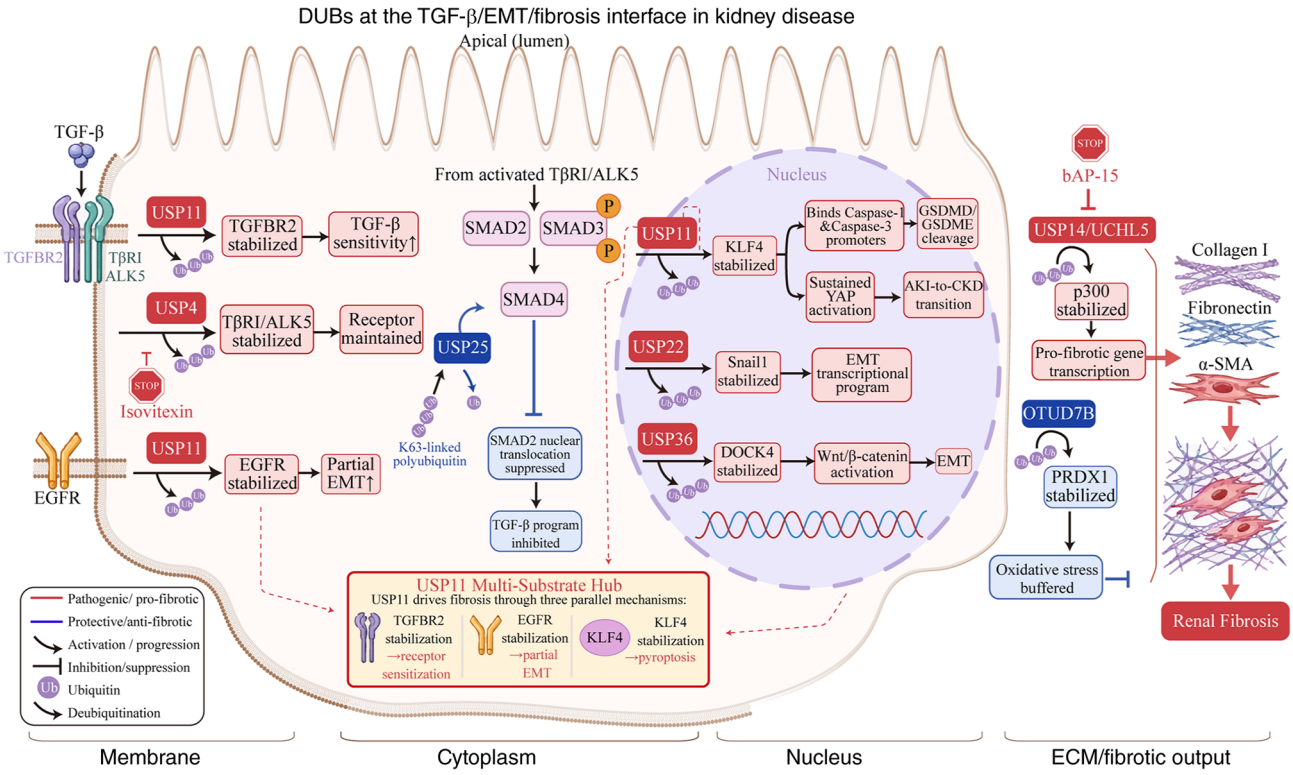

Figure 2. DUBs at the TGF-β/EMT/fibrosis interface in kidney disease. Left-to-right signaling cascade within a renal tubular epithelial cell. Receptor level: USP11 deubiquitinates and stabilizes TGFBR2 and EGFR, sensitizing cells to TGF-β signaling and driving partial EMT; USP4 stabilizes TβRI/ALK5 (isovitexin inhibitor indicated). Cytoplasmic: USP25 removes K63-linked polyubiquitin from SMAD4, suppressing SMAD2 nuclear translocation (protective, blue). Nuclear: USP11-stabilized KLF4 drives pyroptosis via Caspase-1/3 and sustains YAP activation for the AKI-to-CKD transition; USP22 stabilizes Snail1 for EMT; USP36 stabilizes DOCK4 for Wnt/β-catenin activation. USP11 multi-substrate hub (highlighted): three parallel mechanisms converge on fibrosis. ECM: USP14/UCHL5 stabilize p300 (bAP-15); OTUD7B stabilizes PRDX1 (protective). DUB, deubiquitinating enzyme; EMT, epithelial-to-mesenchymal transition.

ferroptosis, pyroptosis and necroptosis, contributes to tubular injury in AKI and promotes maladaptive repair during CKD progression. Previous studies have implicated several DUBs in the regulation of these processes, primarily through modulating mitochondrial outer membrane proteins, antioxidant defenses and key mediators of programmed cell death (48,72-75).

DUBs in mitochondrial quality control. USP14, a proteasome-associated DUB, suppresses mitophagy through stabilization of the transcription factor *Tfap2a* (AP-2α) via deubiquitination in renal tubular epithelial cells, which represses Tbk1 transcription (76). *Tbk1* encodes TANK-binding kinase 1, an essential regulator of mitophagy initiation. In murine I/R models, USP14 silencing reduced serum creatinine and blood urea nitrogen, attenuated oxidative stress and preserved tubular architecture. USP14 inhibition or knockdown also suppressed reactive oxygen species-mediated ferroptotic cell death in HK-2 cells (77). These dual effects on mitophagy and ferroptosis position USP14 as a potential target in ischemic AKI, although current evidence is limited to experimental models and awaits validation in human disease.

USP13 acts in opposition: It is downregulated in AKI patient kidneys and cisplatin-challenged mice. USP13 deubiquitinates and stabilizes MCL-1, a pro-survival member of the Bcl-2 family that maintains mitochondrial outer membrane stability (78). Genetic deletion or pharmacological inhibition of USP13 aggravated kidney injury, whereas overexpression was protective. The USP13-MCL-1 axis represents an endogenous protective pathway whose loss during AKI may increase tubular susceptibility to mitochondrial dysfunction (79).

DUBs in ferroptosis. Accumulating evidence indicates that ferroptosis, a lipid peroxidation-dependent and iron-dependent mode of regulated cell death, contributes to AKI and DKD. Several DUBs have recently been implicated in the regulation of ferroptotic responses in the kidney, though in several cases the evidence comes from single studies using single models. OTUD5 was reported to be recruited to autophagosomes during ferroptosis induction and degraded, relieving its deubiquitination of GPX4 and thereby permitting ferroptosis (80). In cisplatin-induced AKI, a SIRT6/BAP1/xCT signaling axis was shown to participate in the regulation of ferroptosis (81). USP18 was shown to promote ferroptosis in LPS-treated human kidney organoids by deubiquitinating and stabilizing STING1 (82). In DKD, USP38 was found to enhance ferroptotic injury in tubular epithelial cells, whereas pharmacological or genetic inhibition of USP38 alleviated tubular damage in diabetic mouse models (83,84).

These ferroptosis-related findings illustrate a broader point: Numerous DUB-ferroptosis associations have been reported in a single model or cell type. Cross-validation across independent models and correlation with human tissue would help distinguish robust findings from model-specific observations.

DUBs in pyroptosis. The USP11-KLF4-pyroptosis axis (Section 4) provides the most detailed characterization of a DUB-pyroptosis connection in the kidney. The JOSD2-SIRT7-p65 pathway links an MJD family DUB to NF-κB-driven inflammation and cell death in AKI (43). For necroptosis, indirect connections exist several of the DUBs discussed in the present review regulate RIPK1 ubiquitination status, which determines whether TNFR1 signaling proceeds toward NF-κB activation or necroptosis but direct functional studies of DUBs in renal necroptosis are largely absent (85,86).

6. DUBs in podocyte homeostasis and injury

Podocytes are terminally differentiated epithelial cells whose loss is a hallmark of progressive glomerular disease (87). Several DUBs have been functionally characterized in podocytes across diabetic, hypertensive and autoimmune glomerular disease models (Fig. 2) (88-90).

OTUD5 is downregulated in podocytes following exposure to high glucose and palmitic acid, and its expression is likewise reduced in the kidneys of both type 1 and type 2 diabetic mouse models. Podocyte-specific *Otud5* knockout exacerbated foot process effacement, proteinuria and glomerulosclerosis. Conversely, AAV9-mediated OTUD5 overexpression in podocytes reduced albuminuria and preserved glomerular structure. OTUD5 removes K63-linked polyubiquitin from TAK1 at K158 via Cys224, preventing TAK1 phosphorylation and downstream MAPK/NF-κB activation (42). The OTUD5-TAK1 axis is currently the best-characterized podocyte-protective DUB pathway, though its role has been examined primarily by a single group in diabetic models, and independent validation across other models is still lacking.

Beyond its tubular functions (Section 3), A20 is essential for podocyte homeostasis. Podocyte-specific A20 knockout leads to spontaneous glomerular injury with elevated serum urea and creatinine, podocyte loss, and inflammatory cell infiltration (53). A20 also protects against glomerulonephritis severity, with effects on both inflammatory signaling and cytoskeletal integrity.

OTUB1, an OTU family DUB with K48-linkage specificity, is significantly downregulated in podocytes of lupus nephritis patients (confirmed in biopsies) and in MRL/lpr lupus-prone mice. Moreover, OTUB1 expression shows an inverse association with disease severity. CRISPR-mediated OTUB1 knockout decreased nephrin and podocin expression while increasing ferroptosis markers. Ferrostatin-1 rescued OTUB1-deficient podocytes and ameliorated renal histopathology and proteinuria in murine lupus nephritis (91). USP22 has also been reported to promote podocyte injury in diabetic nephropathy by triggering ACSL4 deubiquitination (92), extending the pathogenic role of USP22 from tubular EMT (Section 4) to podocyte injury.

7. DUBs in RCC

RCC, especially the clear cell subtype (ccRCC), is closely linked to ubiquitin-proteasome system regulation. The defining genetic lesion in ccRCC is biallelic inactivation of VHL, which encodes the substrate-recognition component of an E3 ubiquitin ligase complex responsible for oxygen-dependent HIFα degradation (20). In VHL-deficient tumors, HIFα particularly HIF2α escapes ubiquitination and accumulates, driving angiogenesis, glycolysis and proliferation. The DUBs that regulate HIFα stability, as well as those acting on VHL-independent oncogenic pathways, have drawn interest as potential therapeutic targets. The renal DUB landscape therefore encompasses a natural continuum from non-malignant kidney disease (where DUBs control injury, inflammation, and fibrosis) to malignancy (where DUBs regulate oncogenic protein stability and tumor suppression) (Fig. 3).

DUBs that stabilize HIF2α. USP7 was identified through proteomic profiling as significantly upregulated in ccRCC tumors. The transcription factors FUBP1 and FUBP3 activate USP7 expression; USP7 in turn deubiquitinates and stabilizes HIF2α (93). USP7 knockdown or pharmacological inhibition (P5091, P22077) suppressed proliferation of VHL-mutant ccRCC lines and xenograft growth. Combining the USP7 inhibitor P5091 with afatinib which suppresses FUBP-mediated USP7 transcription produced synergistic HIF2α suppression and extended survival in PDX models. Together, these findings support a pro-tumorigenic role for USP7 in VHL-deficient ccRCC, largely through maintenance of the HIF2α transcriptional program. USP37 was independently identified as an additional HIF2α-directed DUB, with its depletion reducing ccRCC proliferation and metastasis in orthotopic models (94). The existence of at least two DUBs capable of stabilizing HIF2α suggests potential redundancy that could influence the efficacy of single-DUB targeting strategies. However, USP7 exhibits substrate- and context-dependent functions in ccRCC. In addition to promoting tumor progression through HIF2α stabilization, USP7 has been reported to exert tumor-suppressive effects through TRIP12 deubiquitination and induction of pyroptosis (95). Therefore, the biological outcome of USP7 modulation may depend on the relative contribution of individual substrates and cellular contexts. This dual functionality represents an important consideration for therapeutic development, as complete inhibition of USP7 activity may simultaneously suppress oncogenic signaling while interfering with potentially protective pathways.

VHL-independent oncogenic DUBs. USP13 was identified through a DUB cDNA library screen as the enzyme that deubiquitinates and stabilizes ZHX2, a transcription factor that functions as a HIF-independent substrate of pVHL (96). USP13 depletion reduced ZHX2 levels and inhibited ccRCC growth *in vitro* and *in vivo*, defining a VHL/HIF-parallel oncogenic pathway. USP28, initially characterized in ADPKD (Section 8), also promotes ccRCC growth (97). USP52 was reported to promote ccRCC progression through deubiquitination of CORO6, an actin-binding protein implicated in migration (98).

UCHL1, a UCH family member, was identified as a mediator of axitinib resistance in ccRCC through deubiquitination and stabilization of MMP9 (99), linking DUB activity to anti-angiogenic therapy resistance.

Tumor-suppressive DUBs in RCC include BAP1, which is mutated in a subset of ccRCC and functions through histone H2A deubiquitination and HIF-dependent interferon-β induction (100).

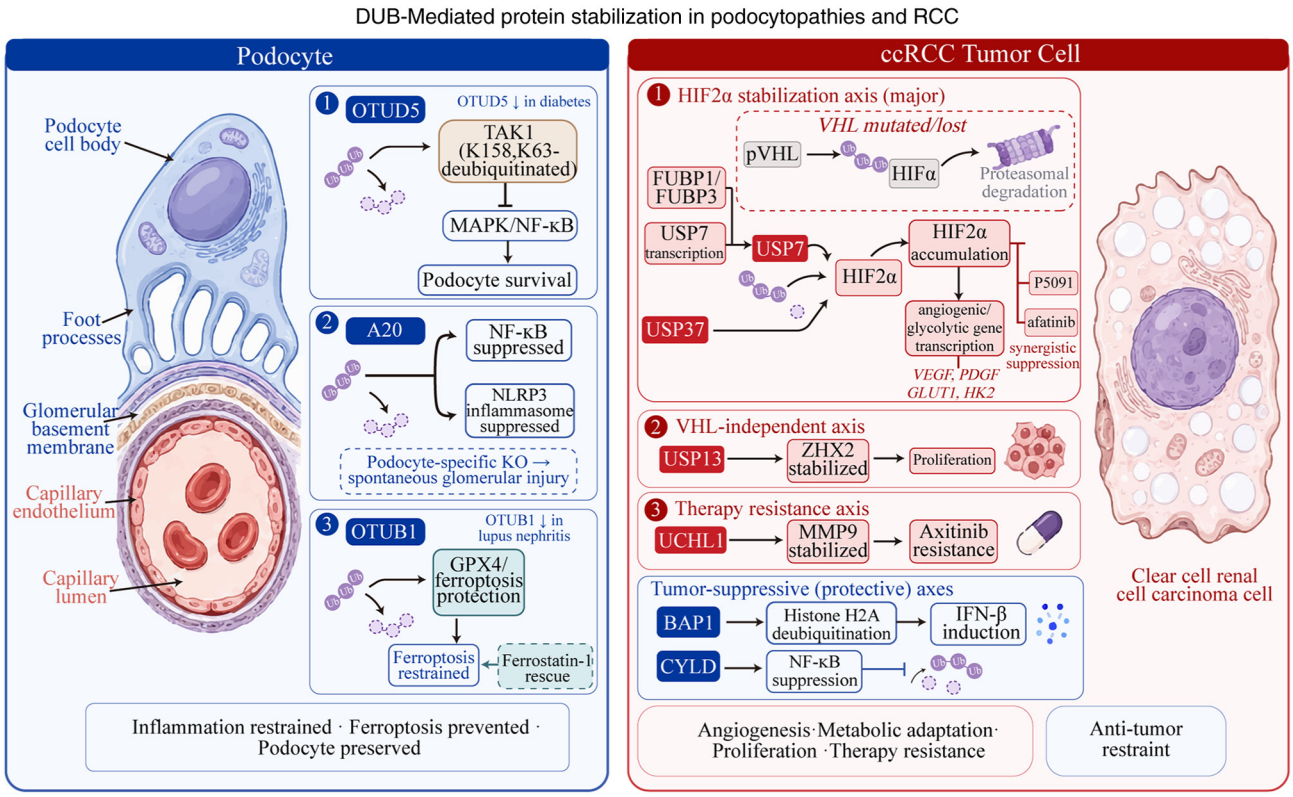

Figure 3. DUB-mediated protein stabilization in podocytopathies and RCC. Two-panel comparative schematic. Left (podocyte): OTUD5 deubiquitinates TAK1 at K158 to suppress MAPK/NF-κB (protective, downregulated in diabetes); A20 suppresses NF-κB and NLRP3 inflammasome; OTUB1 protects against ferroptosis (downregulated in lupus nephritis; ferrostatin-1 rescue). Right (ccRCC): HIF2α stabilization axis-FUBP1/3 transcriptionally activate USP7, which deubiquitinates HIF2α (USP37 provides parallel stabilization; P5091 plus afatinib synergy indicated); VHL-independent axis-USP13 stabilizes ZHX2; therapy resistance-UCHL1 stabilizes MMP9 (axitinib resistance). Tumor-suppressive DUBs: BAP1 (histone H2A deubiquitination; IFN-β induction) and CYLD (NF-κB suppression). DUB, deubiquitinating enzyme; RCC, renal cell carcinoma; ccRCC, clear cell RCC; VHL, von Hippel-Lindau.

8. DUBs in other kidney conditions

USP28 has been linked to the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). Increased USP28 expression has been observed in samples from patients with ADPKD, where it removes K48-linked chains from STAT3 and c-Myc, stabilizing both proteins. The dual stabilization drives cyst-lining epithelial cell proliferation and cyst growth (101). Pharmacological inhibition of USP28 reduced cyst development in *Pkd1*-mutant mouse models, providing the first evidence for a DUB as a target in ADPKD; confirmatory studies from additional groups are awaited.

In kidney transplantation, USP33 has emerged as a differentially expressed DUB associated with an autophagy-related gene signature capable of distinguishing antibody-mediated rejection from other forms of graft dysfunction (102). The functional role of USP33 in allograft rejection has not been experimentally determined. A comprehensive catalog of DUBs with established roles in kidney disease, organized by disease category, cell type and functional effect, is provided in Table I.

9. Translational landscape

The therapeutic targeting of DUBs has progressed from concept to clinical evaluation over the past decade (71,103,104). Progress has been aided by ubiquitin-based activity probes, advances in DUB structural biology, and fragment-based screening methods suited to DUB active sites (103-105). The DUB-substrate axes with the strongest preclinical rationale for therapeutic or diagnostic translation are summarized in Table II, along with their current evidence levels and key limitations.

For renal applications, several preclinical-stage targets have emerged. USP11 inhibitors (mitoxantrone) showed anti-fibrotic efficacy in the UUO model (33), though mitoxantrone also inhibits other DUBs and its selectivity profile requires further characterization. USP14 has been targeted with IU1 in renal I/R models (76,77). The USP14/UCHL5 inhibitor bAP-15 suppressed EMT *in vitro* (38). USP1 and USP30 inhibitors, already in clinical development for other indications, could be evaluated for renal conditions where mitophagy modulation is relevant.

Two emerging modalities expand the DUB targeting toolkit. PROTACs (proteolysis-targeting chimeras) enable selective degradation rather than catalytic inhibition of DUBs, eliminating both enzymatic and scaffolding functions. DUBTACs (deubiquitinase-targeting chimeras), developed by the Nomura and Jin laboratories, recruit specific DUBs to proteins of interest, inducing deubiquitination and stabilization (106). In the kidney, DUBTACs could theoretically stabilize protective proteins such as nephrin or podocin, though this application has not been explored experimentally.

Table I. Representative DUBs in kidney disease organized by disease category.

First author/s, year	Disease	DUB	Cell type	Substrate/pathway	Effect	(Refs.)
Wang *et al*, 2025; Shi *et al*, 2023; Ni *et al*, 2023	CKD/Fibrosis	USP11	Tubular epithelial cell	KLF4, TGFBR2, EGFR	Pathogenic	(33,66,67)
Zhao *et al*, 2023	CKD/Fibrosis	USP25	Tubular epithelial cell	SMAD4/TGF-β	Protective	(34)
Liu *et al*, 2023	DKD	USP25	Mesangial cell, macrophage	TRAF6/NF-κB-MAPK	Protective	(35)
Wang *et al*, 2024	CKD/Fibrosis	OTUD1	Tubular epithelial cell	CDK9/transcription	Pathogenic	(41)
Zhao *et al*, 2024	DKD	OTUD5	Podocyte	TAK1/MAPK-NF-κB	Protective	(42)
Zhao *et al*, 2025	AKI (I/R, cisplatin)	JOSD2	Tubular epithelial cell	SIRT7/NF-κB	Protective	(43)
Rogers *et al*, 2023; Köhler *et al*, 2025; Li *et al*, 2025	AKI/Glomerular inflammation	A20	Tubular epithelial cell, podocyte	NF-κB, NLRP3	Protective	(52-54)
Tachizaki *et al*, 2024	CKD/Fibrosis	CYLD	Tubular epithelial cell	TLR3/NF-κB	Protective	(56)
Luo *et al*, 2023	AKI (sepsis)	BAP1	Tubular epithelial cell	BRCA1/NF-κB	Protective	(57)
Gong *et al*, 2024	AKI (sepsis)	USP9x	Tubular epithelial cell	TLR4/NF-κB	Pathogenic	(59)
Zhao *et al*, 2024	AKI (sepsis)	USP10	Tubular epithelial cell	FOXQ1-CREB5/NF-κB	Protective	(62)
Xiong *et al*, 2026	CKD/Fibrosis	OTUD7B	Tubular epithelial cell	PRDX1/oxidative stress	Protective	(68)
Zhao *et al*, 2023	CKD/Fibrosis	USP22	Tubular epithelial cell	Snail1/EMT	Pathogenic	(69)
	DKD	USP22	Tubular epithelial cell, podocyte	ACSL4/ferroptosis	Pathogenic	(92)
Zhu *et al*, 2021	DKD	USP36	Tubular epithelial cell	DOCK4/Wnt-β-cat	Pathogenic	(70)
Fan *et al*, 2026	CKD/Fibrosis	USP4	Tubular epithelial cell	TbRI/TGF-β	Pathogenic	(71)
Li *et al*, 2024; Pan *et al*, 2023	AKI (I/R)	USP14	Tubular epithelial cell	Tfap2a-TBK1/mitophagy; ROS-dependent Ferroptosis	Pathogenic	(76,77)
Wang *et al*, 2025	AKI (Cisplatin)	USP13	Tubular epithelial cell	MCL-1/apoptosis	Protective	(78)
Gao *et al*, 2026	DKD	USP38	Tubular epithelial cell	Ferroptosis mediator	Pathogenic	(83)
Liu *et al*, 2024	LN	OTUB1	Podocyte	Ferroptosis regulation/ SLC7A11-GSH axis	Protective	(91)
Hong *et al*, 2020	RCC	USP37	Clear cell RCC	HIF-2α/metastasis	Pathogenic	(94)
Tu *et al*, 2024	RCC	USP7	Clear cell RCC	HIF-2α/angiogenesis	Pathogenic	(93)
Xie *et al*, 2022	RCC	USP13	Clear cell RCC	ZHX2/proliferation	Pathogenic	(96)
Wang *et al*, 2025	RCC	UCHL1	Clear cell RCC	MMP9/axitinib resist	Pathogenic	(99)
Langbein *et al*, 2022	RCC	BAP1	Clear cell RCC	H2A, IFN-β	Tumor suppressive	(100)

Table I. Continued.

First author/s, year	Disease	DUB	Cell type	Substrate/pathway	Effect	(Refs.)
Ren *et al*, 2023	ADPKD	USP28	Cyst epithelial cell	STAT3, c-Myc	Pathogenic	(101)
Xu *et al*, 2024	Transplant	USP33	Not determined	Autophagy signature	Biomarker only	(102)

ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; DKD, diabetic kidney disease; RCC, renal cell carcinoma; LN, lupus nephritis; DUB, deubiquitinating enzyme; HIF, hypoxia-inducible factor.

Critical therapeutic challenges. Several challenges remain before DUB-based therapies can be translated into clinical applications in nephrology. A major consideration is the context-dependent biological function of individual DUBs, in which a single enzyme may regulate multiple substrates with distinct or even opposing effects depending on cellular context, disease stage, and tissue environment. For example, USP7 promotes ccRCC progression through HIF2α stabilization but may also exert tumor-suppressive effects through TRIP12-mediated pyroptosis (95). Therefore, the therapeutic challenge is not simply whether USP7 should be inhibited, but rather how to selectively modulate disease-associated USP7 activities while preserving potentially protective functions. This highlights the importance of defining substrate-specific interactions, cellular context, and disease-specific vulnerabilities when developing USP7-targeted therapies. Similar considerations apply to other DUBs with context-dependent functions, emphasizing the need for precision modulation rather than indiscriminate inhibition.

Selectivity within DUB families remains another major obstacle. Although DUBs represent attractive therapeutic targets because of their well-defined catalytic domains and druggable enzymatic activities, achieving sufficient selectivity remains challenging, particularly within the USP family containing ~56 members with highly conserved catalytic regions (104). Off-target inhibition of related DUBs may lead to unexpected biological effects and compromise therapeutic safety. Future development of selective DUB modulators will require integration of structural biology, substrate-recognition profiling, activity-based probes, and chemical optimization to identify compounds that distinguish disease-relevant DUB functions from physiological ubiquitin regulation (104,107).

Furthermore, emerging targeted protein regulation platforms, including PROTACs (proteolysis-targeting chimeras) and DUBTACs (deubiquitinase-targeting chimeras), provide new opportunities beyond conventional enzymatic inhibition. PROTACs induce selective degradation of target proteins by recruiting E3 ubiquitin ligases, whereas DUBTACs promote stabilization of specific proteins by recruiting endogenous DUB activity (108). However, the clinical translation of these approaches faces substantial pharmacokinetic and pharmaceutical challenges. Compared with conventional small-molecule inhibitors, PROTACs and DUBTACs generally exhibit larger molecular sizes and complex physicochemical properties, which may result in limited membrane permeability, reduced oral bioavailability, rapid clearance and insufficient tissue penetration (108,109). These 'beyond-rule-of-five' characteristics complicate absorption, distribution, metabolism and pharmacodynamic optimization, thereby representing important barriers for clinical development.

For kidney diseases, an additional challenge is whether these macromolecular agents can achieve sufficient exposure within specific renal compartments, including tubular epithelial cells, podocytes and interstitial fibroblasts. Currently, limited information is available regarding renal biodistribution, intracellular delivery efficiency, metabolism and long-term safety profiles of PROTACs and DUBTACs. Therefore, strategies that improve tissue penetration and cell-type specificity will be essential for successful renal application of these emerging platforms.

Table II. Translational DUB axes: Diagnostic and therapeutic potential.

First author/s, year	DUB/axis	Potential application	Model/disease	Current evidence	Limitations	(Refs.)
Wang *et al*, 2025	USP11-KLF4-Caspase	Anti-fibrotic therapy (AKI-to-CKD)	UUO mouse; Ang II-treated renal tubular epithelial cells	KO + mitoxantrone reduce pyroptosis/fibrosis	Mitoxantrone non-selective; human data lacking	(33)
Zhao *et al*, 2023; Liu *et al*, 2023	USP25-SMAD4/TRAF6	Anti-fibrotic + anti-inflammatory	Ang II, STZ mouse	KO aggravates; AAV9-OE protects	Therapeutic activation of DUB is technically challenging	(34,35)
Zhao *et al*, 2024	OTUD5-TAK1 (podocyte)	Podocyte protection in DKD	T1DM, T2DM mouse	cKO aggravates; AAV9-OE protects	Single-group validation; delivery to podocytes	(42)
Li *et al*, 2025	A20 peptide (P-II)	Anti-inflammatory in AKI	Mouse AKI model	Peptide reduces AKI by disrupting NEK7-NLRP3	Peptide stability/delivery; single study	(54)
Li *et al*, 2024; Pan *et al*, 2023	USP14-Tfap2a-mitophagy	AKI prevention (I/R, transplant)	Mouse I/R model	IU1 or siRNA reduce Cr/BUN, enhance mitophagy	USP14 dual role (ferroptosis); proteasome function	(76,77)
Wang *et al*, 2025	USP13-MCL-1	Mitochondrial protection in AKI	Cisplatin mouse	KO aggravates; OE protects	Limited to cisplatin model; human data single study	(78)
Tu *et al*, 2024; Li *et al*, 2025	USP7-HIF-2α (FUBP-USP7)	Anti-angiogenic therapy (ccRCC)	ccRCC cell lines, xenograft, PDX	P5091 + afatinib synergy extends PDX survival	USP7 dual role (TRIP12); selectivity vs. other USPs	(93,95)
Ren *et al*, 2023	USP28-STAT3/c-Myc	Anti-cystic therapy (ADPKD)	ADPKD patient tissue, Pkd1 mouse	Inhibitor attenuates cyst growth	Single study; dual substrate complexity	(101)
Xu *et al*, 2024	USP33	Diagnostic biomarker (ABMR)	Kidney transplant biopsies	Part of autophagy signature distinguishing ABMR	No functional validation; single cohort	(102)

AKI, acute kidney injury; CKD, chronic kidney disease; DKD, diabetic kidney disease; ccRCC, clear cell renal cell carcinoma; UUO, unilateral ureteral obstruction; DUB, deubiquitinating enzyme; HIF, hypoxia-inducible factor; BUN, blood urea nitrogen.

Kidney-targeted delivery approaches, such as megalin-mediated nanoparticle systems, may provide a potential solution by increasing renal accumulation while reducing systemic exposure and off-target toxicity. This consideration is particularly relevant for dual-function DUBs such as USP25, which has been implicated in both inflammatory regulation and renal injury progression. Global USP25 inhibition may theoretically suppress pathological inflammatory signaling while simultaneously interfering with protective immune regulatory pathways. Therefore, kidney- or cell-specific delivery strategies may enable selective modulation of pathogenic DUB activity within diseased renal compartments while minimizing unwanted effects in extra-renal tissues.

10. Future directions

Several actionable priorities emerge from the current state of the field. First, to overcome selectivity challenges, it is recommended using high-throughput screening methods that target allosteric sites rather than conserved catalytic pockets. Second, future studies should prioritize single-cell RNA sequencing and spatial transcriptomics on human kidney biopsies to validate findings from animal models and resolve cell-type-specific DUB functions. Third, most studies have focused on K48- and K63-linked ubiquitination; the six other linkage types and heterotypic chain architectures remain unexplored in renal DUB biology.

The AKI-to-CKD transition is a natural focus for future DUB research. The USP11-KLF4 axis (33,110) illustrates how sustained DUB activity after an initial injury can drive maladaptive repair. Whether other DUBs participate in determining the balance between regeneration and fibrosis after AKI is not known. The DUBTAC platform conceptually enables therapeutic protein stabilization in kidney disease, but its application to renal targets has not been explored.

Clinical translation will require progress in medicinal chemistry for renal DUB inhibitors, preclinical validation in large-animal kidney disease models, and biomarker development to match DUB-targeted therapies to appropriate patient subgroups. Consortia such as the Kidney Precision Medicine Project may generate comprehensive tissue-level datasets that enable the association of DUB expression patterns to molecularly defined disease subtypes (111). Finally, it is essential to include target-engagement biomarkers in early-phase clinical trials for DUB degraders (PROTACs/DUBTACs) to accurately measure their *in vivo* efficacy.

11. Conclusion

Deubiquitinating enzymes have emerged as an important regulatory component that shapes diverse biological processes in kidney physiology and disease. Rather than functioning as generic regulators of protein stability, individual DUBs operate as relatively narrow, substrate-defined nodes that control specific pathological processes. The functional division between protective DUBs (A20, CYLD, USP25, OTUD5, USP13, JOSD2 and OTUB1) and pathogenic DUBs (USP11, OTUD1, USP14, USP22, USP36 and USP7) provides a framework for therapeutic development.

The translational landscape is tempered by selectivity challenges, the dual tissue roles of numerous DUBs, and the need for kidney-targeted delivery. Progress in DUB structural biology, chemical biology (PROTACs and DUBTACs), and spatial proteomics provides the technological foundation for addressing these challenges. As the field moves from isolated mechanistic studies toward integrated understanding, DUBs may transition from an underexplored regulatory dimension to a clinically actionable target class in nephrology.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Sichuan Science and Technology Program (grant no. 2025ZNSFSC0617), the Joint Project of Luzhou Municipal People's Government and Southwest Medical University (grant no. 2025LZXNYDJC05) and the Funding Program of Southwest Medical University (grant no. 2023ZYYJ02).

Availability of data and materials

Not applicable.

Authors' contributions

QL wrote the original draft, organized the literature and prepared the figures and tables. ZL wrote the original draft and assisted with figure and table preparation. YN contributed to literature collection and manuscript drafting. JL and LW wrote, reviewed and edited the manuscript, supervised the study and acquired funding. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. GBD Chronic Kidney Disease Collaboration: Global, regional, and national burden of chronic kidney disease, 1990-2017: A systematic analysis for the Global Burden of disease study 2017. Lancet 395: 709-733, 2020.
2. Webster AC, Nagler EV, Morton RL and Masson P: Chronic kidney disease. Lancet 389: 1238-1252, 2017.
3. Humphreys BD: Mechanisms of renal fibrosis. Annu Rev Physiol 80: 309-326, 2018.
4. Liu Y: Kidney fibrosis: Fundamental questions, challenges, and perspectives. Integr Med Nephrol Androl 11: e24, 2024.
5. Chawla LS, Eggers PW, Star RA and Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 371: 58-66, 2014.
6. Zou Y, Dai J, Li J, Liu M, Li R, Li G, Lai J and Wang L: Role of the TGF-β/Smad signaling pathway in the transition from acute kidney injury to chronic kidney disease (Review). Int J Mol Med 56: 162, 2025.
7. Liao Y, Lin X, Li J, Tan R, Zhong X and Wang L: Nodakenin alleviates renal ischaemia-reperfusion injury via inhibiting reactive oxygen species-induced NLRP3 inflammasome activation. Nephrology (Carlton) 26: 78-87, 2021.
8. Tan RZ, Li JC, Liu J, Lei XY, Zhong X, Wang C, Yan Y, Linda Ye L, Darrel Duan D, Lan HY and Wang L: BAY61-3606 protects kidney from acute ischemia/reperfusion injury through inhibiting spleen tyrosine kinase and suppressing inflammatory macrophage response. FASEB J: Sep 15, 2020 doi: 10.1096/fj.202000261RRR (Epub ahead of print).
9. Alicic RZ, Rooney MT and Tuttle KR: Diabetic kidney disease: Challenges, progress, and possibilities. Clin J Am Soc Nephrol 12: 2032-2045, 2017.
10. Zou Y, Guo X and Liu S: Metabolites mediate the causal associations between gut microbiota and chronic kidney disease: A Mendelian randomization study and therapeutical strategy from traditional Chinese medicine perspective. Integr Med Nephrol Androl 12: e24, 2025.
11. Jin Q and Zhan Y: Traditional Chinese medicine as a promising therapy for patients with membranous nephropathy. Integr Med Nephrol Androl 12: e25, 2025.
12. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS and Hobbs FDR: Global prevalence of chronic kidney disease-a systematic review and meta-analysis. PLoS One 11: e0158765, 2016.
13. Liyanage T, Toyama T, Hockham C, Ninomiya T, Perkovic V, Woodward M, Fukagawa M, Matsushita K, Praditpornsilpa K, Hooi LS, *et al*: Prevalence of chronic kidney disease in Asia: A systematic review and analysis. BMJ Glob Health 7: e007525, 2022.
14. Deng Y, Li N, Wu Y, Wang M, Yang S, Zheng Y, Deng X, Xiang D, Zhu Y, Xu P, *et al*: Global, regional, and national burden of diabetes-related chronic kidney disease from 1990 to 2019. Front Endocrinol (Lausanne) 12: 672350, 2021.
15. Du Z, Chen W, Xia Q, Shi O and Chen Q: Trends and projections of kidney cancer incidence at the global and national levels, 1990-2030: A Bayesian age-period-cohort modeling study. Biomark Res 8: 16, 2020.
16. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A and Anders HJ: Acute kidney injury. Nat Rev Dis Primers 7: 52, 2021.
17. Shao B and Wei B: Glycolysis-driven renal fibrosis in chronic kidney disease: Emerging mechanisms and therapeutic opportunities. Integr Med Nephrol Androl 12: e25, 2025.
18. Wang H, Dhaliwal NS, Zahin M, Zhao T, Sims GL, Xie J and Zheng G: The clinical effectiveness of Anti-TGF-β therapy in chronic kidney disease: A systematic review of western and traditional Chinese medicine. Integr Med Nephrol Androl 12: e24, 2025.
19. Komander D and Rape M: The ubiquitin code. Annu Rev Biochem 81: 203-229, 2012.
20. Kaelin WG Jr: The von Hippel-Lindau tumour suppressor protein: O2 sensing and cancer. Nat Rev Cancer 8: 865-873, 2008.
21. Komander D, Clague MJ and Urbé S: Breaking the chains: Structure and function of the deubiquitinases. Nat Rev Mol Cell Biol 10: 550-563, 2009.
22. Kwasna D, Abdul Rehman SA, Natarajan J, Matthews S, Madden R, De Cesare V, Weidlich S, Virdee S, Ahel I, Gibbs-Seymour I and Kulathu Y: Discovery and characterization of ZUFSP/ZUP1, a distinct deubiquitinase class important for genome stability. Mol Cell 70: 150-164.e6, 2018.
23. Lu D, Zhang Y, Zhu P, Wu J, Yuan C and Ni L: The roles of the ubiquitin-proteasome system in renal disease. Int J Med Sci 22: 1791-1810, 2025.
24. Nijman SMB, Luna-Vargas MPA, Velds A, Brummelkamp TR, Dirac AMG, Sixma TK and Bernards R: A genomic and functional inventory of deubiquitinating enzymes. Cell 123: 773-786, 2005.
25. Clague MJ, Barsukov I, Coulson JM, Liu H, Rigden DJ and Urbé S: Deubiquitylases from genes to organism. Physiol Rev 93: 1289-1315, 2013.
26. Meyer-Schwesinger C: The ubiquitin-proteasome system in kidney physiology and disease. Nat Rev Nephrol 15: 393-411, 2019.
27. Yau R and Rape M: The increasing complexity of the ubiquitin code. Nat Cell Biol 18: 579-586, 2016.
28. Reyes-Turcu FE, Ventii KH and Wilkinson KD: Regulation and cellular roles of ubiquitin-specific deubiquitinating enzymes. Annu Rev Biochem 78: 363-397, 2009.
29. Swatek KN and Komander D: Ubiquitin modifications. Cell Res 26: 399-422, 2016.
30. Wu X, Liu S, Sagum C, Chen J, Singh R, Chaturvedi A, Horton JR, Kashyap TR, Fushman D, Cheng X, *et al*: Crosstalk between Lys63- and Lys11-polyubiquitin signaling at DNA damage sites is driven by Cezanne. Genes Dev 33: 1702-1717, 2019.
31. Clague MJ, Urbé S and Komander D: Breaking the chains: Deubiquitylating enzyme specificity begets function. Nat Rev Mol Cell Biol 20: 338-352, 2019.
32. Faesen AC, Luna-Vargas MPA and Sixma TK: The role of UBL domains in ubiquitin-specific proteases. Biochem Soc Trans 40: 539-545, 2012.
33. Wang X, Xie X, Ni JY, Li JY, Sun XA, Xie HY, Yang NH, Guo HJ, Lu L, Ning M, *et al*: USP11 promotes renal tubular cell pyroptosis and fibrosis in UUO mice via inhibiting KLF4 ubiquitin degradation. Acta Pharmacol Sin 46: 159-170, 2025.
34. Zhao Y, Chen X, Lin Y, Li Z, Su X, Fan S, Chen Y, Wang X and Liang G: USP25 inhibits renal fibrosis by regulating TGFβ-SMAD signaling pathway in Ang II-induced hypertensive mice. Biochim Biophys Acta Mol Basis Dis 1869: 166713, 2023.
35. 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: 110877, 2023.
36. Larsen CN, Price JS and Wilkinson KD: Substrate binding and catalysis by ubiquitin C-terminal hydrolases: Identification of two active site residues. Biochemistry 35: 6735-6744, 1996.
37. Peña-Llopis S, Vega-Rubín-de-Celis S, Liao A, Leng N, Pavía-Jiménez A, Wang S, Yamasaki T, Zhrebker L, Sivanand S, Spence P, *et al*: BAP1 loss defines a new class of renal cell carcinoma. Nat Genet 44: 751-759, 2012.
38. Kim H, Kim H, Lee SH, Kwon JH, Byun S, Yoo JY, Park SY and Yoon HG: Deubiquitinase inhibitor bAP-15 suppresses renal epithelial to mesenchymal transition via inhibition of p300 stability. Biochem Biophys Res Commun 741: 151095, 2024.
39. Mevissen TET, Hospenthal MK, Geurink PP, Elliott PR, Akutsu M, Arnaudo N, Ekkebus R, Kulathu Y, Wauer T, El Oualid F, *et al*: OTU deubiquitinases reveal mechanisms of linkage specificity and enable ubiquitin chain restriction analysis. Cell 154: 169-184, 2013.
40. Wiener R, Zhang X, Wang T and Wolberger C: The mechanism of OTUB1-mediated inhibition of ubiquitination. Nature 483: 618-622, 2012.
41. Wang MY, Yu TX, Wang QY, Han X, Hu X, Ye SJ, Long XH, Wang Y, Zhu H, Luo W and Liang G: OTUD1 promotes hypertensive kidney fibrosis and injury by deubiquitinating CDK9 in renal epithelial cells. Acta Pharmacol Sin 45: 765-776, 2024.
42. Zhao Y, Fan S, Zhu H, Zhao Q, Fang Z, Xu D, Lin W, Lin L, Hu X, Wu G, *et al*: Podocyte OTUD5 alleviates diabetic kidney disease through deubiquitinating TAK1 and reducing podocyte inflammation and injury. Nat Commun 15: 5441, 2024.
43. Zhao Y, Zhao QQ, Fan SJ, Xu DY, Lin LM, Luo W, Ye BZ, Zou CP, Zhu H, Zhuang ZS, *et al*: JOSD2 alleviates acute kidney injury through deubiquitinating SIRT7 and negativity regulating SIRT7-NF-κB inflammatory pathway in renal tubular epithelial cells. Acta Pharmacol Sin 46: 2468-2481, 2025.
44. 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.

45. Verma R, Aravind L, Oania R, McDonald WH, Yates JR, Koonin EV and Deshaies RJ: Role of Rpn11 metalloprotease in deubiquitination and degradation by the 26S proteasome. Science 298: 611-615, 2002.
46. Hermanns T, Pichlo C, Woiwode I, Klopffleisch K, Witting KF, Ovaa H, Baumann U and Hofmann K: A family of unconventional deubiquitinases with modular chain specificity determinants. Nat Commun 9: 799, 2018.
47. Lee K, Jang HR and Rabb H: Lymphocytes and innate immune cells in acute kidney injury and repair. Nat Rev Nephrol 20: 789-805, 2024.
48. Zhou Y, Tao S, Liu L and Zhang L: The role of Ubiquitination and Deubiquitination in the pathogenesis of acute kidney injury: Progress in research. Biomedicines 13: 2873, 2025.
49. Jang HR and Rabb H: Immune cells in experimental acute kidney injury. Nat Rev Nephrol 11: 88-101, 2015.
50. Lee SA, Noel S, Sadasivam M, Hamad ARA and Rabb H: Role of immune cells in acute kidney injury and repair. Nephron 137: 282-286, 2017.
51. Wertz IE, O'Rourke KM, Zhou H, Eby M, Aravind L, Seshagiri S, Wu P, Wiesmann C, Baker R, Boone DL, *et al*: De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signalling. Nature 430: 694-699, 2004.
52. Rogers NM, Zammit N, Nguyen-Ngo D, Souilmi Y, Minhas N, Meijles DN, Self E, Walters SN, Warren J, Cultrone D, *et al*: The impact of the cytoplasmic ubiquitin ligase TNFAIP3 gene variation on transcription factor NF-κB activation in acute kidney injury. Kidney Int 103: 1105-1119, 2023.
53. Köhler P, Ribeiro A, Honarpisheh M, von Rauchhaupt E, Lorenz G, Li C, Martin L, Steiger S, Lindenmeyer M, Schmaderer C, *et al*: Podocyte A20/TNFAIP3 controls glomerulonephritis severity via the regulation of inflammatory responses and effects on the cytoskeleton. Cells 14: 381, 2025.
54. Li H, Wu Y, Xiang L, Zhao Q, Liu L, Zhu Z, Lin W, Li Z, Yang Y, Ze Y, *et al*: A20 attenuates oxidized self-DNA-mediated inflammation in acute kidney injury. Signal Transduct Target Ther 10: 154, 2025.
55. Sun SC: CYLD: A tumor suppressor deubiquitinase regulating NF-kappaB activation and diverse biological processes. Cell Death Differ 17: 25-34, 2010.
56. Tachizaki M, Kobori Y, Kawaguchi S, Seya K, Tanaka H and Imaizumi T: Cylindromatosis lysine 63 deubiquitinase (CYLD) suppress TLR3-mediated CCL5 expression in human renal proximal tubular epithelial cells. Mol Biol Rep 51: 974, 2024.
57. Luo S, Gong J, Zhao S, Li M and Li R: Deubiquitinase BAP1 regulates stability of BRCA1 protein and inactivates the NF-κB signaling to protect mice from sepsis-induced acute kidney injury. Chem Biol Interact 382: 110621, 2023.
58. Han B, Zheng Q, Li H, Wang Y and Zhang D: PRDM16 suppresses pyroptosis to attenuate the progression of AKI caused by rhabdomyolysis via upregulation of USP10. Cell Mol Life Sci 82: 138, 2025.
59. Gong S, Xiong H, Lei Y, Huang S, Ouyang Y, Cao C and Wang Y: Usp9x contributes to the development of sepsis-induced acute kidney injury by promoting inflammation and apoptosis in renal tubular epithelial cells via activation of the TLR4/nf-κb pathway. Ren Fail 46: 2361089, 2024.
60. Wang R, Shen Y, Shi J, Huang H, Feng S, Fang X, Gu X and Yu Y: Deubiquitinase USP10 regulates angiotensin II-induced renal fibrosis by modulating the expression of TLR4. Mutat Res 832: 111932, 2026.
61. LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, Woda C, Sugimoto H and Kalluri R: Origin and function of myofibroblasts in kidney fibrosis. Nat Med 19: 1047-1053, 2013.
62. Zhao Q, Zhang R, Wang Y, Li T, Xue J and Chen Z: FOXQ1, deubiquitinated by USP10, alleviates sepsis-induced acute kidney injury by targeting the CREB5/NF-κB signaling axis. Biochim Biophys Acta Mol Basis Dis 1870: 167331, 2024.
63. Distler JHW, Györfi AH, Ramanujam M, Whitfield ML, Königshoff M and Lafyatis R: Shared and distinct mechanisms of fibrosis. Nat Rev Rheumatol 15: 705-730, 2019.
64. Chen Y, Dai R, Cheng M, Wang W, Liu C, Cao Z, Ge Y, Wang Y and Zhang L: Status and role of the ubiquitin-proteasome system in renal fibrosis. Biomed Pharmacother 178: 117210, 2024.
65. Kramann R, Machado F, Wu H, Kusaba T, Hoeft K, Schneider RK and Humphreys BD: Parabiosis and single-cell RNA sequencing reveal a limited contribution of monocytes to myofibroblasts in kidney fibrosis. JCI Insight 3: e99561, 99561, 2018.
66. Shi Y, Tao M, Chen H, Ma X, Wang Y, Hu Y, Zhou X, Li J, Cui B, Qiu A, *et al*: Ubiquitin-specific protease 11 promotes partial epithelial-to-mesenchymal transition by deubiquitinating the epidermal growth factor receptor during kidney fibrosis. Kidney Int 103: 544-564, 2023.
67. Ni JY, Wang X, Xie HY, Yang NH, Li JY, Sun XA, Guo HJ, Zhou L, Zhang W, Liu J and Lu LM: Deubiquitinating enzyme USP11 promotes renal tubular cell senescence and fibrosis via inhibiting the ubiquitin degradation of TGF-β receptor II. Acta Pharmacol Sin 44: 584-595, 2023.
68. Xiong Y, Zhao X, Qin X, Zhang Y, Wang L, Zheng Q, Liu X, Liu H and Chen Z: OTUD7B attenuates renal fibrosis by regulating PRDX1 protein stability. J Adv Res: Mar 5, 2026 doi: 10.1016/j.jare.2026.02.059 (Epub ahead of print).
69. Zhao X, He X, Wei W and Huang K: USP22 aggravated diabetic renal tubulointerstitial fibrosis progression through deubiquitinating and stabilizing Snail1. Eur J Pharmacol 947: 175671, 2023.
70. Zhu S, Hou S, Lu Y, Sheng W, Cui Z, Dong T, Feng H and Wan Q: USP36-mediated deubiquitination of DOCK4 contributes to the diabetic renal tubular epithelial cell injury via Wnt/β-catenin signaling pathway. Front Cell Dev Biol 9: 638477, 2021.
71. Fan J, Liu Y, Zhan S, Ling H, Yan J, Xie L, Wang W, Xiao X and Li A: Targeting USP4 to inhibit TGF-β signaling: The antifibrotic potential of isovitexin in renal interstitial fibrosis. Phytomedicine 155: 158141, 2026.
72. Tang C, Cai J, Yin XM, Weinberg JM, Venkatachalam MA and Dong Z: Mitochondrial quality control in kidney injury and repair. Nat Rev Nephrol 17: 299-318, 2021.
73. Wang Y, Cai J, Tang C and Dong Z: Mitophagy in acute kidney injury and kidney repair. Cells 9: 338, 2020.
74. Pohl C and Dikic I: Cellular quality control by the ubiquitin-proteasome system and autophagy. Science 366: 818-822, 2019.
75. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, *et al*: Molecular mechanisms of cell death: Recommendations of the nomenclature committee on cell death 2018. Cell Death Differ 25: 486-541, 2018.
76. Li Y, Dong B, Wang Y, Bi H, Zhang J, Ding C, Wang C, Ding X and Xue W: Inhibition of Usp14 ameliorates renal ischemia-reperfusion injury by reducing Tfap2a stabilization and facilitating mitophagy. Transl Res 270: 94-103, 2024.
77. Pan J, Zhao J, Feng L, Xu X, He Z and Liang W: Inhibition of USP14 suppresses ROS-dependent Ferroptosis and alleviates renal ischemia/reperfusion injury. Cell Biochem Biophys 81: 87-96, 2023.
78. Wang Q, Cao S, Sun Z, Zhu W, Sun L, Li Y, Luo D, Huang S, Zhang Y, Xia W, *et al*: USP13 inhibition exacerbates mitochondrial dysfunction and acute kidney injury by acting on MCL-1. Biochim Biophys Acta Mol Basis Dis 1871: 167599, 2025.
79. Kaloni D, Diepstraten ST, Strasser A and Kelly GL: BCL-2 protein family: Attractive targets for cancer therapy. Apoptosis 28: 20-38, 2023.
80. Chu LK, Cao X, Wan L, Diao Q, Zhu Y, Kan Y, Ye LL, Mao YM, Dong XQ, Xiong QW, *et al*: Autophagy of OTUD5 destabilizes GPX4 to confer ferroptosis-dependent kidney injury. Nat Commun 14: 8393, 2023.
81. Yang S, Chen L, Din S, Ye Z, Zhou X, Cheng F and Li W: The SIRT6/BAP1/xCT signaling axis mediates ferroptosis in cisplatin-induced AKI. Cell Signal 125: 111479, 2025.
82. Yang H, Zhao L, Kong W, Liu S, Zhou Q, Lang X, Lan L and Wang Y: USP18 promotes ferroptosis in lipopolysaccharide-induced human kidney organoids by stabilizing STING1. Cell Biol Toxicol 41: 126, 2025.
83. Gao S, Dong C, Li H, Li J and Abula A: Inhibiting ubiquitin-specific protease 38 safeguards against diabetic nephropathy by limiting tubular epithelial cell ferroptotic death through the suppression of IREB2-mediated iron overload. Int Immunopharmacol 173: 116307, 2026.
84. Battaglia AM, Chirillo R, Aversa I, Sacco A, Costanzo F and Biamonte F: Ferroptosis and cancer: Mitochondria meet the 'Iron Maiden' cell death. Cells 9: 1505, 2020.
85. Shi J, Gao W and Shao F: Pyroptosis: Gasdermin-mediated programmed necrotic cell death. Trends Biochem Sci 42: 245-254, 2017.
86. Popper B, Rammer MT, Gasparitsch M, Singer T, Keller U, Döring Y and Lange-Sperandio B: Neonatal obstructive nephropathy induces necroptosis and necroinflammation. Sci Rep 9: 18600, 2019.

87. Kriz W and Lemley KV: A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. J Am Soc Nephrol 26: 258-269, 2015.
88. Wu Y, Jia H, Sun F, Yang Y, Li Z and Liu WJ: E3 ubiquitin ligases and deubiquitinases: Promising therapeutic targets for diabetic kidney disease. Cell Signal 143: 112513, 2026.
89. Mima A, Nomura A and Yasuzawa T: Update on the pathophysiology and treatment of diabetic kidney disease: A narrative review. Expert Rev Clin Immunol 21: 921-928, 2025.
90. Hou G, Dong Y, Jiang Y, Zhao W, Zhou L, Cao S and Li W: Immune inflammation and metabolic interactions in the pathogenesis of diabetic nephropathy. Front Endocrinol (Lausanne) 16: 1602594, 2025.
91. Liu C, Gan YH, Yong WJ, Xu HD, Li YC, Hu HM, Zhao ZZ and Qi YY: OTUB1 regulation of ferroptosis and the protective role of ferrostatin-1 in lupus nephritis. Cell Death Dis 15: 791, 2024.
92. Wang X, Wang W, Han M, Zhang J and Li Y: ELAVL1-stabilized USP22 promotes diabetic nephropathy progression via mediating podocyte injury and death by triggering ACSL4 deubiquitination. Transpl Immunol 93: 102280, 2025.
93. Tu R, Ma J, Chen Y, Kang Y, Ren D, Cai Z, Zhang R, Pan Y, Liu Y, Da Y, *et al*: USP7 depletion potentiates HIF2α degradation and inhibits clear cell renal cell carcinoma progression. Cell Death Dis 15: 749, 2024.
94. Hong K, Hu L, Liu X, Simon JM, Ptacek TS, Zheng X, Liao C, Baldwin AS and Zhang Q: USP37 promotes deubiquitination of HIF2α in kidney cancer. Proc Natl Acad Sci USA 117: 13023-13032, 2020.
95. Li H, Ning Y, Yu J, Chen Y, He Q and Jin J: USP7 overexpression prevents the progression of clear cell renal cell carcinoma by enhancing pyroptosis via TRIP12 deubiquitination. Cancer Biol Ther 26: 2558402, 2025.
96. Xie H, Zhou J, Liu X, Xu Y, Hepperla AJ, Simon JM, Wang T, Yao H, Liao C, Baldwin AS, *et al*: USP13 promotes deubiquitination of ZHX2 and tumorigenesis in kidney cancer. Proc Natl Acad Sci USA 119: e2119854119, 2022.
97. Ren Y, Yang Y, Zhu X, Li L, Pan Y, Sun H, Fang Q, Xiong H, Guo D, Sun Y, *et al*: Targeting USP28 inhibits clear cell renal cell carcinoma growth. Cell Signal 139: 112344, 2026.
98. Wang X, Zhang N, Bu Y, Zhang Y, Wang X, He X, Zhuang X, Zong Q, Zhou B and Luo G: USP52 promotes clear cell renal carcinoma progression by deubiquitinating and stabilizing CORO6. Transl Oncol 68: 102773, 2026.
99. Wang Z, Chen L, Zhang H, Yan Z, Liu K, Qi J, Lu B, Yin Y, Zhao C, Niu Y and Li W: Mechanism of NUMBL enhancing axitinib resistance in clear cell renal cell carcinoma by UCHL1-mediated deubiquitination of MMP9. J Biol Chem 301: 110873, 2025.
100. Langbein LE, El Hajjar R, He S, Sementino E, Zhong Z, Jiang W, Leiby BE, Li L, Uzzo RG, Testa JR and Yang H: BAP1 maintains HIF-dependent interferon beta induction to suppress tumor growth in clear cell renal cell carcinoma. Cancer Lett 547: 215885, 2022.
101. Ren Y, Zhu X, Fu K, Zhang H, Zhao W, Lin Y, Fang Q, Wang J, Chen Y and Guo D: Inhibition of deubiquitinase USP28 attenuates cyst growth in autosomal dominant polycystic kidney disease. Biochem Pharmacol 207: 115355, 2023.
102. Xu Y, Wang Y, Zhang D, Zhang H, Wang Y, Wang W and Hu X: An autophagy-associated diagnostic signature based on peripheral blood for antibody-mediated rejection in renal transplantation. Transpl Immunol 84: 102021, 2024.
103. Liu P, Chen Z, Guo Y, He Q and Pan C: Recent advances in small molecule inhibitors of deubiquitinating enzymes. Eur J Med Chem 287: 117324, 2025.
104. Harrigan JA, Jacq X, Martin NM and Jackson SP: Deubiquitylating enzymes and drug discovery: Emerging opportunities. Nat Rev Drug Discov 17: 57-78, 2018.
105. Yang X, Lan T, Zhang B, Tao X, Qi W, Xie K, Cai Y, Liu C, Han J and Wu H: Targeting ubiquitination in disease and therapy. Signal Transduct Target Ther 10: 424, 2025.
106. Henning NJ, Boike L, Spradlin JN, Ward CC, Liu G, Zhang E, Belcher BP, Brittain SM, Hesse MJ, Dovala D, *et al*: Deubiquitinase-targeting chimeras for targeted protein stabilization. Nat Chem Biol 18: 412-421, 2022.
107. 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.
108. Békés M, Langley DR and Crews CM: PROTAC targeted protein degraders: The past is prologue. Nat Rev Drug Discov 21: 181-200, 2022.
109. Chamberlain PP and Hamann LG: Development of targeted protein degradation therapeutics. Nat Chem Biol 15: 937-944, 2019.
110. Xu D, Chen PP, Zheng PQ, Yin F, Cheng Q, Zhou ZL, Xie HY, Li JY, Ni JY, Wang YZ, *et al*: KLF4 initiates sustained YAP activation to promote renal fibrosis in mice after ischemia-reperfusion kidney injury. Acta Pharmacol Sin 42: 436-450, 2021.
111. El-Achkar TM, Eadon MT, Kretzler M and Himmelfarb J; Kidney Precision Medicine Project: Precision medicine in nephrology: An integrative framework of multidimensional data in the kidney precision medicine project. Am J Kidney Dis 83: 402-410, 2024.