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Review Article

OTU deubiquitinases in cancer pathogenesis and precision therapy

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Abstract: The OTU family consists of 16 highly conserved deubiquitinases (DUBs) that play critical roles in regulating diverse signaling pathways through substrate-specific deubiquitination of key proteins. These enzymes are involved in multiple physiological processes, including cancer progression, immune responses, cell division, and inflammation modulation. Depending on their target substrates, individual OTU family members perform distinct functions across biological processes, as exemplified by their dual roles in cancer pathogenesis. Increasing attention has been directed toward developing OTU DUB inhibitors as potential cancer therapeutics. This review provides a systematic analysis of recent structural and functional studies on OTU family members, with a particular focus on their roles in cancer. We discuss their associations with various malignancies and summarize advances in OTU-targeted inhibitor development, emphasizing their clinical potential as novel therapeutic targets.

Keywords: Deubiquitination, ovarian tumor domain, environmentally dependent oncogene, cancer progression, immunity

Introduction

Ubiquitination is an important post-translational modification of proteins and is involved in the regulation of many cellular processes, including protein hydrolysis, macromolecular transport, DNA damage repair, cell proliferation, receptor signaling, cellular communication, and immune recognition processes [1]. This process is a sequential enzymatic reaction in which ubiquitin is covalently attached to target proteins [2]. Importantly, ubiquitination of proteins is a reversible process. Coupling ubiquitin by forming a homopeptide bond between the C-terminus of ubiquitin and the substrate protein usually requires the involvement of three enzymes, including ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligase (E3), and is removed by deubiquitinizing enzyme (DUB) [3, 4]. Ubiquitin ligase (E3) is antagonized by deubiquitinase (DUB), which can remove the ubiquitin chain or inhibit the catalytic function of ubiquitin-associated enzymes, thus inhibiting the ubiquitination process [5] (**Figure 1**). Each ubiquitin molecule contains eight potential modification sites: seven lysine residues (K6, K11, K27, K29, K33, K48, and K63) and the N-terminal methionine (Met1) [6, 7]. In contrast, deubiquitinating enzymes (DUBs) remove ubiquitin from substrate proteins, edit ubiquitin chains, and process ubiquitin precursors, a process known as deubiquitination [8]. Deubiquitinating enzymes can regulate the dynamic balance between ubiquitination and deubiquitination in organisms by participating in the process of ubiquitination. An imbalance between ubiquitination and deubiquitination in organisms can lead to a variety of diseases, cancer being one of the important

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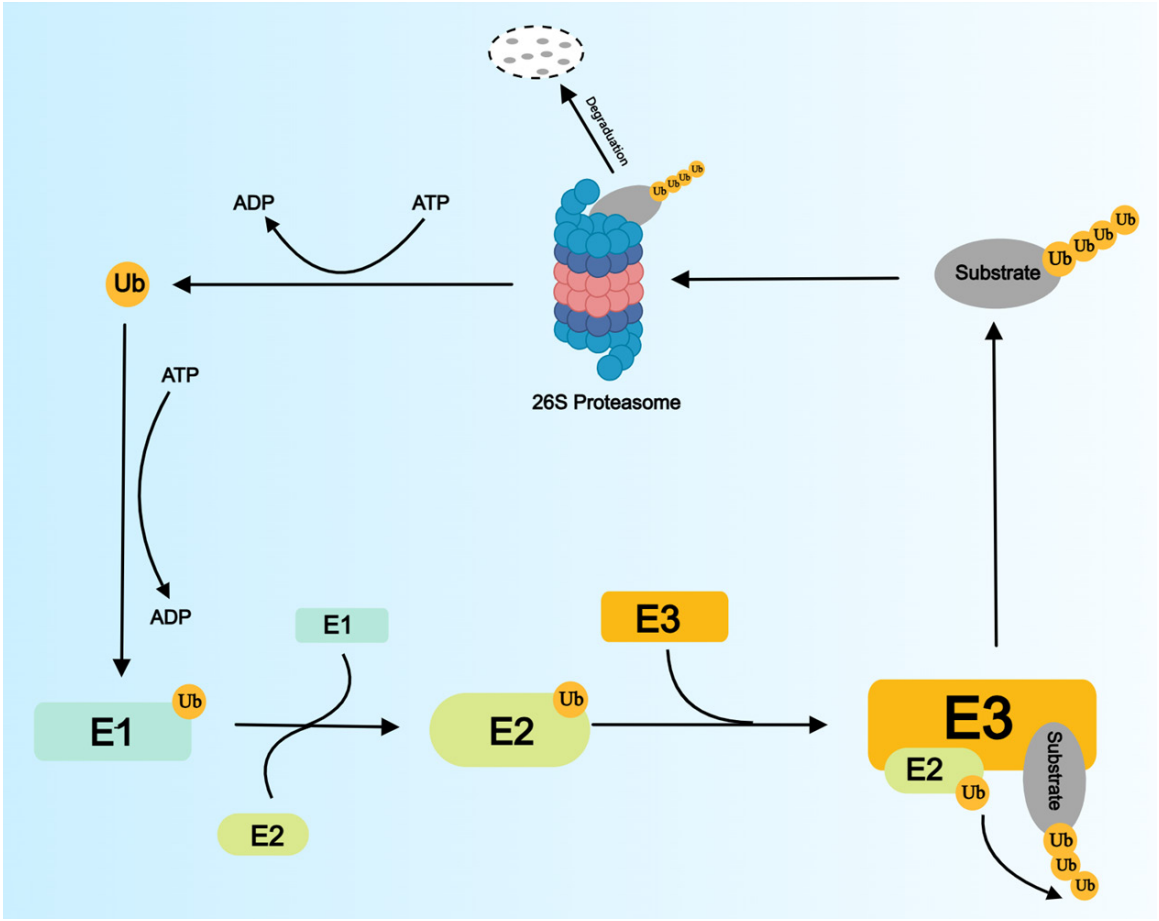


Figure 1. Ubiquitination is an ATP-dependent post-translational modification (PTM) performed by three enzymes, E1, E2 and E3.

ones [9]. Increasing evidence indicates that the processes of protein ubiquitination and deubiquitination are closely associated with various cancers, including breast cancer, non-small cell lung cancer, and hepatocellular carcinoma [10].

The human genome encodes approximately 100 deubiquitinating enzymes (DUBs), which are categorized into seven families: ubiquitin-specific proteases (USPs), ovarian tumor (OTU) proteases, JAMM/MPN domain-associated Zn-dependent metalloproteases (JAMMs), ubiquitin C-terminal hydrolases (UCHs), zinc finger (ZnF)-containing ubiquitin peptidase 1 (ZUP1), and ubiquitin-containing proteases (MINDYs) [11, 12].

The OTU family represents the second-largest deubiquitinating enzyme (DUB) family in humans. Based on protein structure, OTUs are classified into four subfamilies: (1) the OTUD subfamily, comprising proteins with OTU structural domains (OTUD1, OTUD2/YOD1, OTUD3, OTUD4, OTUD5/D ubiquitin-associated (UBA), OTUD6A, OTUD6B, and ALG13); (2) the otubain subfamily, consisting of ubiquitin aldehyde-binding proteins that contain OTU structural domains (OTUB1 and OTUB2); (3) the A20-like subfamily, including A20, OTUD7A, OTUD7B, TRAPID, and VCPIP1; and (4) the OTULIN subfamily, which exhibits linear ubiquitin chain specificity [13] (**Figure 2**). OTU-type DUBs demonstrate remarkable selectivity for specific ubiquitin chains, highlighting their capacity to recognize and act on particular types of ubiquitin linkages [14, 15].

In this review, we review the structural features of OTU family and their regulatory mechanisms and functions in different tumors. We provide a concise overview of the context-dependent roles of OTU family members in cancer, and further explore the possibility of OTU family as therapeutic targets in tumor diagnosis and treatment.

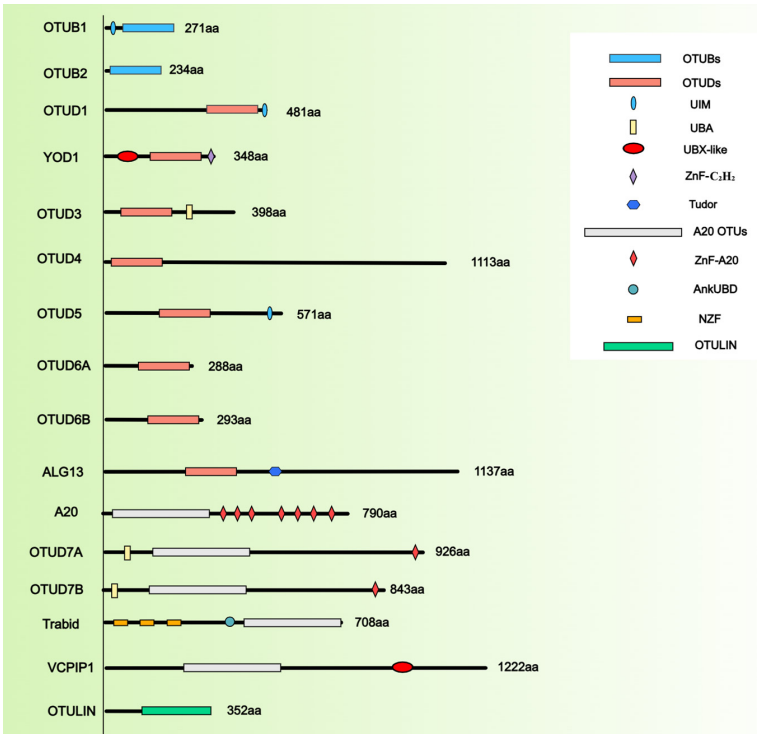


Figure 2. Schematic illustration of OTU family architectures.

Structural features

OTU

Almost all OTU family members contain an OTU catalytic domain and a ubiquitin-binding domain, relying on a cysteine (Cys103) residue in the catalytic triad to process ubiquitin. OTUs generally exhibit low activity in vitro, requiring specific conditions provided by the cellular environment for full activation. Conformational changes in the catalytic triad are essential for their enzymatic function. OTU-type DUBs also display marked selectivity for particular ubiquitin chains, highlighting their ability to specifically recognize and process distinct ubiquitin linkages [14]. Structurally, the OTU core domain consists of β-strands flanked by α-helices and can be divided into three regions: the pre-α-helical domain, central β-sandwich domain, and post-α-helical domain [16, 17]. Despite structural diversity among OTU deubiquitinases (DUBs), the arrangement of catalytic residues is highly conserved. Individual OTU family members also show preferences for specific polyubiquitin chain linkages [18]. Importantly, different ubiquitin chain types carry distinct functional implications: K48-linked chains primarily signal proteasomal degradation, whereas K63-linked chains mainly mediate protein-protein interactions and regulate a variety of cellular processes [19]. These ubiquitin chains play critical roles in numerous biological contexts, including cancer progression, neurodegenerative diseases, signal transduction, autophagy, DNA damage response, and innate immunity [19, 20].

The otubain subfamily (OTUB1 and OTUB2)

OTUB1: OTUB1 is among the most abundant DUBs in cells and exhibits a strong preference for K48- over K63-linked ubiquitin chains. This DUB employs a unique non-canonical mechanism: its N-terminal ubiquitin-binding domain allows direct interaction with E2 ubiquitin-conjugating enzymes. Through this interaction, OTUB1 stabilizes the E2~ubiquitin complex and potently inhibits ubiquitination in a DUB activity-independent manner by blocking ubiquitin transfer from E2 to substrate proteins [21, 22]. For example, OTUB1 directly engages the E2 complex RNF168/UBC13 to suppress histone ubiquitination [23]. It also uses this non-canonical mechanism to stabilize RACK1 by preventing its ubiquitination, thereby promoting lung tumorigenesis [24]. In addition, OTUB1 can perform canonical deubiquitination through its intrinsic enzymatic activity, directly removing ubiquitin from substrate proteins. A notable example is its deubiquitination of YAP, which attenuates Hippo pathway signaling and promotes gastric cancer proliferation and metastasis [25]. Beyond cancer, OTUB1 regulates a variety of pathological processes, including ferroptosis [26, 27], NK/CD8$^+$ T-cell activation [28], PD-L1-mediated immune evasion [29], autoimmune disorders [29, 30], as well as infections by IAV [31] and HBV [32].

OTUB2: Compared with OTUB1, OTUB2 shares approximately 70% sequence similarity and 48% sequence identity [33]. Structurally, OTUB2 contains only a C-terminal OTU catalytic domain and exhibits distinct preferences for K48-, K6-, and K11-linked ubiquitin chains [14].

OTUB2 contributes to oncogenesis by modulating multiple signaling pathways, including the Hippo pathway [34, 35], nuclear factor kappa B (NF-κB) transcriptional control [36, 37], and Akt/mechanistic target of rapamycin (mTOR) metabolic signaling [38]. Moreover, OTUB2 plays pivotal roles in DNA repair and immune regulation. Notably, it mediates DNA repair processes through specific cleavage of RNF8-catalyzed K63-linked polyubiquitin chains on L3MBTL1, thereby suppressing DNA end resection [39]. OTUB2 further modulates antiviral immunity by deubiquitinating TRAF6 to attenuate cellular antiviral responses [40], while concurrently stabilizing PD-L1 to facilitate tumor immune evasion [41]. Previous studies have demonstrated that OTUB2 facilitates tumor progression via the Warburg effect, a process mediated through the deubiquitination of substrates like PKM2 and U2AF2 and the subsequent activation of the AKT/mTOR pathway [38, 42, 43].

OTUDs

OTUD1: OTUD1 is a 481-amino-acid Cys103 protease that contains a UIM domain and plays a key role in regulating K63-linked ubiquitination. It is involved in diverse biological processes, including immune responses [44], cell growth and apoptosis [45], enhancement of host anti-tumor immunity [46], and chemoresistance [47]. For example, OTUD1 regulates cell growth and apoptosis by deubiquitinating p53 [45]. It also interacts with Smurf1 to deubiquitinate and enhance Smurf1 expression, promoting the degradation of the MAVS/TRAF3/TRAF6 complex and thereby suppressing the innate immune response to viral infections [48]. Furthermore, OTUD1 deubiquitinates AIF and stabilizes DCAF10 and DDB1, activating a Cys103 protease-independent apoptotic pathway in cells [16].

OTUD2/YOD1: OTUD2, also known as YOD1, is a cysteine protease consisting of 348 amino acids [13]. Its protein contains three conserved structural domains: the N-terminal UBX structural domain, the central OTU structural domain, and the C-terminal C_2H_2-type ZnF structural domain [49, 50]. The OTU structural domain contains conserved cysteine, aspartate, and histidine residues, which constitute the catalytic triad of cysteine proteases [51]. The UBX structural domain is essential for mediating ubiquitin ligase TRAF6 interactions to counteract IL-1 signaling to the NF-κB pathway [52]. The Znf structural domain of YOD1 is deubiquitylated through direct binding to CDK1 and clears Ub through the OTUD structural domain, with regulation of enzymatic activity typical of the cell cycle [53]. As a deubiquitinating enzyme, the catalytic structural domain of OTUD2 is biased towards cleavage of the k11 chain [14].

YOD1 is involved in endoplasmic reticulum (ER)-related degradation pathways [50], Clearance of damaged lysosomes [54] and the regulation of multiple biological activities such as antigen cross-presentation [55]. YOD1 interacts with the ubiquitin ligase TRAF6 to counteract IL-1 signaling to the NF-κB pathway [52].

OTUD3: OTUD3 is a 398-amino-acid Cys103 protease in humans [13]. It is highly evolutionarily conserved and contains an OTU domain as well as a UBA domain. The UBA domain is a short-sequence motif composed of compact triple-helix bundles and large hydrophobic surface patches, which enable binding to ubiquitin as well as other proteins lacking obvious ubiquitin-like structures [56]. The specific functions of the N-terminal and C-terminal regions of OTUD3 remain unclear due to missing structural data. As a deubiquitinating enzyme, OTUD3 preferentially cleaves K6- and K63-linked ubiquitin chains, and to a lesser extent, K11- and K48-linked chains [57]. OTUD3 activity is regulated by acetylation at Lys129: under resting conditions, Lys129 acetylation significantly enhances its ability to hydrolyze K63-linked ubiquitin chains, whereas during viral infection, SIRT1 is recruited to OTUD3 and deacetylates Lys129, thereby inactivating the enzyme [58].

Recent studies have also identified OTUD3 as a key regulator of glucose and lipid metabolism, with dysfunction of OTUD3 being associated with an increased risk of obesity and diabetes mellitus [59]. Additionally, OTUD3 contributes to neuroprotection by stabilizing IRP2, thereby preventing Parkinson's disease [60].

OTUD4: OTUD4 consists of 1113 amino acids, and it has only one OTU structural domain [13], However, OTUD4 carries a triad consisting of serine and aspartic acid with histidine rather than cysteine with the latter two [61]. OTUD4 favors cleavage of K48-linked polyubiquitin

chains [13], Whereas phosphorylation of the Ser202/204 site of OTUD4 activates its dormant K63-specific DUB activity [62].

OTUD4 is composed of 1113 amino acid residues and contains only one OTU domain. As a deubiquitinating enzyme that preferentially cleaves K48-linked ubiquitin chains, it stabilizes the MAVS protein by cleaving such chains. This process maintains the antiviral response at a specific level, thereby activating the antiviral immune response [63]. Phosphorylation in the vicinity of the catalytic domain of OTUD4 activates its dormant K63-specific deubiquitinating enzyme activity, enabling it to regulate MyD88-dependent signal transduction [60]. Evolutionarily, the OTUD4 homologous proteins in most species retain the catalytic cysteine residue. However, the Drosophila homologs CG3251 and Otu carry a triad consisting of serine, aspartic acid, and histidine instead of cysteine paired with the latter two amino acids [61], which results in the loss of enzymatic activity in these proteins. Nevertheless, experimental evidence has demonstrated that CG3251 is capable of regulating the process of cell apoptosis [61]. Moreover, previous studies have indicated that OTUD4 acts as a scaffold protein, which binds to both ALKBH3 and USP7/USP9X simultaneously through its DRD domain, thereby forming a multi-deubiquitinase complex. This complex collectively facilitates the deubiquitination and stabilization of the alkylation repair enzyme ALKBH3 via a non-canonical mechanism that is independent of its own catalytic activity [64]. This may indicate that the catalytic activity of OTUD4 is non-essential under certain scenarios.

OTUD5: OTUD5 is a member of the OTUD subfamily of deubiquitinases, consisting of 571 amino acids, which contains an ovarian tumor structural domain (OTU) and a UIM structural domain [13]. UIM is an interaction site for STING, SPT16, TRIM25, P53 and PDCD5 [65-67]. OTUD5 favors cleavage of K48- and K63-linked polyubiquitin chains [68, 69]. It has been reported that phosphorylation of a single residue Ser177 on OTUD5 is sufficiently necessary for activation of OTUD5, pSer177 forms a salt bridge network with the C-terminal tail of ubiquitin and the internal basic helix α6 of OTUD5. This network promotes OTUD5 to "embrace" ubiquitin and adopt a closed conformation, which indirectly activates the enzymatic activity of OTUD5 by stabilizing the enzyme-substrate complex [70]. In addition, OTUD5 is ubiquitinated and degraded by RNF146, which is also the only E3 ligase found to act with OTUD5 [71].

OTUD5 was originally identified as a negative regulator of type I interferon [72]. In recent years, OTUD5 plays an important role in the progression of immune diseases and inflammation [73, 74]. Recently, the role of OTUD5 in ferroptosis has also attracted increasing attention, and OTUD5 ameliorates MI/R-induced ferroptosis and cardiac injury [75]. Important role in the regulation of I/R-induced acute kidney injury (AKI) and subsequent cellular ferroptosis [76], OTUD5 also enhances hepatocellular carcinoma cell stemness by stabilizing SLC7A11 upregulating c-Myc expression [77]. Additionally, studies have found that the expression of OTUD5 in hepatocellular carcinoma is relatively complex. Research indicates that OTUD5 not only exhibits pro-carcinogenic properties in hepatocellular carcinoma [66], but also demonstrates tumor-suppressive effects [78].

OTUD6A and OTUD6B: Within the OTUD subfamily, OTUD6A and OTUD6B share the highest homology. Compared with OTUD6B, research on OTUD6A has been relatively limited, but significant progress has been made in recent years. OTUD6A has been shown to play an essential role in the development of inflammation [79, 80] and innate immunity [81]. Additionally, it has been implicated in promoting various cancers, including prostate cancer [82, 83], breast cancer [84], colorectal cancer [85], as well as renal cell carcinoma and NSCLC [86].

OTUD6B consists of three isoforms. OTUD6B-1 contains an N-terminal coiled-coil domain, while OTUD6B-2 lacks this structure. OTUD6B-3 features a short N-terminal deletion. In NSCLC, OTUD6B-1 and OTUD6B-2 exhibit opposing functions [87]. Furthermore, OTUD6B plays a crucial role in several cancers, including lung adenocarcinoma [88], multiple myeloma [89], laryngeal squamous cell carcinoma [90], hepatocellular carcinoma [91], and clear cell renal carcinoma [92].

ALG13: ALG13 plays an important role in the N-linked glycosylation pathway [93], and mutations in ALG13 have been associated with congenital disorder of glycosylation (CDG), a rare

inherited metabolic disorder. ALG13-Congenital Disorder of Glycosylation (CDG) is an x-linked CDG, which occurs as a result of an x-linked mutation in the X chromosome located in the It occurs due to a de novo or genetic missense variant in the ALG13 gene located on the X chromosome [94]. It manifests as impairment of neurologic function, including symptoms such as seizures, intellectual disability, decreased muscle tone, ataxia, and cerebellar abnormalities [95]. However, the function and mechanism of ALG13 in cancer have not yet been unveiled and remain to be further explored.

A20-like subfamily

A20: A20 is a 790-amino-acid protein comprising an N-terminal OTU domain and seven C-terminal ZnF domains. This dual-function enzyme exhibits both DUB activity, mediated by the catalytic Cys103 in its OTU domain, and E3 ubiquitin ligase activity through its ZnF domains [96, 97]. The fourth ZnF domain (ZnF4) confers E3 ligase activity with a strong preference for K63-linked polyubiquitin chains [98, 99], whereas the seventh ZnF domain (ZnF7) shows pronounced specificity for Met1 (M1)-linked polyubiquitin chains [100, 101].

A20 plays context-dependent roles in oncogenesis, acting as a tumor promoter in breast cancer [102] and melanoma [103], while serving as a tumor suppressor in lymphoma [104, 105] and HCC [106]. Additionally, A20, also known as TNFα-induced protein 3 (TNFAIP3), is a well-characterized negative regulator of NF-κB signaling and inflammatory responses [107].

OTUD7A and OTUD7B: OTUD7A and OTUD7B share a conserved domain architecture consisting of an OTU domain, a UBA domain, and a ZnF motif, representing the only known DUBs with remarkable specificity for K11-linked ubiquitin chains [14]. OTUD7A plays critical roles in central nervous system (CNS) development and function, with genetic studies identifying it as a key pathogenic driver of 15q13.3 microdeletion syndrome [108]. Notably, both OTUD7A and OTUD7B can recognize and process K11/K63-branched ubiquitin chains, a mechanism essential for DNA damage response and repair [109].

OTUD7B exhibits selective cleavage preferences for K11-, K48-, and K63-linked ubiquitin chains [110]. It serves as a key regulator of NF-κB and mTOR signaling pathways, activating mTOR complex 2 (mTORC2) complex assembly and subsequent AKT signaling through GβL deubiquitination, which promotes the GβL-SIN1 interaction [111]. OTUD7B also functions as a negative regulator of the non-canonical NF-κB pathway via TRAF3 deubiquitination [112]. It is frequently overexpressed and demonstrates potent oncogenic activity in multiple malignancies, including gastric, pancreatic, breast, and lung cancers [113-116]. Conversely, OTUD7B exerts tumor-suppressive effects in HCC by deubiquitinating and stabilizing p53, thereby inhibiting cancer progression [117]. Emerging evidence also highlights a cardioprotective role for OTUD7B, whereby HNF4α deubiquitination modulates cell survival and fatty acid oxidation to attenuate cardiac hypertrophy [118].

Trabid: Trabid (ZRANB1) contains three tandem N-terminal NZF domains and exhibits high specificity for cleaving K29- and K33-linked ubiquitin chains, as well as K29/K48-branched chains [119, 120]. Trabid acts as a positive regulator of Wnt/β-catenin signaling by directly interacting with and deubiquitinating the antigen-presenting cell (APC) tumor suppressor protein [121]. It has been associated with poor prognosis in several cancers, including triple-negative breast cancer (TNBC) and colorectal carcinoma [122, 123], although its role in liver cancer remains controversial [124, 125]. Additionally, Trabid contributes to immunotherapeutic responses by inhibiting mitosis and autophagy, thereby activating the cGAS-STING innate immunity pathway [126].

VCPIP1: VCPIP1 contains an N-terminal OTU domain, a central UFD1 domain, and a C-terminal UBL domain. It was initially identified as a p97/VCP-interacting protein, and its DUB activity is essential for p97/VCP-p47-mediated Golgi vesicle fusion during late mitosis [127]. VCPIP1 interacts with p97 through reciprocal binding between its N- and C-terminal domains and the corresponding C- and N-terminal domains of p97 [128]. Recent studies have also shown that VCPIP1 suppresses MDP-induced NF-κB activation and proinflammatory cytokine release by deubiquitinating and stabilizing Erbin in macrophages [129].

OTULIN

OTULIN is currently recognized as the only deubiquitinase (DUB) capable of specifically cleav-

ing Met1-linked ubiquitin chains. It employs a unique substrate-assisted catalytic mechanism that ensures exclusive cleavage of Met1 linkages without affecting other ubiquitin chain types [130]. OTULIN exhibits high affinity for the Met1 S1' site, and binding to this site positions the Met1 residue of proximal ubiquitin near the catalytic active center [130]. OTULIN serves as a critical negative regulator of inflammation by binding the HOIP subunit of LUBAC, thereby counteracting LUBAC-mediated ubiquitination and subsequent NF-κB pathway activation [131, 132]. The OTULIN-LUBAC interaction critically regulates autophagy [133], angiogenesis [134], as well as cell death and inflammatory responses [135].

The role of OTU family members in regulating multiple signaling pathways

Members of the OTU family influence cancer progression and development through diverse signaling pathways and mechanisms, including the PI3K/Akt/mTOR pathway, Wnt/β-catenin signaling, epithelial-mesenchymal transition (EMT), Hippo/YAP pathway, and NF-κB pathway.

PI3K/Akt/mTOR pathway

The PI3K-Akt pathway is aberrantly activated in numerous cancers and serves as a central signaling axis across different tumor types [136]. It not only regulates multiple tumor-associated markers but also plays a critical role in the tumor microenvironment (TME) and angiogenesis. Aberrant activation of the PI3K-Akt pathway can result from mutations in various genes, including PTEN, Akt, TSC1, and mTOR [137]. PTEN functions as an upstream regulator and tumor suppressor with phosphatase activity, inhibiting Akt by dephosphorylating PIP3 and thereby suppressing tumor development [138]. Beyond tumor suppression, PTEN has also emerged as a key factor in overcoming drug resistance across multiple cancers [139]. The mTOR, a downstream effector of the PI3K-Akt pathway, is an evolutionarily conserved serine/threonine kinase whose overexpression is commonly observed in various malignancies [140]. The mTOR pathway regulates cell proliferation and growth in response to diverse stimuli, playing a pivotal role in cancer progression [141]. mTOR functions as two distinct complexes, mTOR complex 1 (mTORC1) and mTORC2. Given its central role in tumorigenesis, inhibitors targeting key components of the PI3K-Akt-mTOR pathway have been actively developed.

Recent studies have demonstrated that OTUB1 employs a non-canonical deubiquitination mechanism to stabilize RACK1 protein levels, thereby activating RACK1-dependent PI3K/Akt and FAK/ERK signaling cascades that drive HCC proliferation and metastasis [24]. OTUB2 is markedly overexpressed in NSCLC tissues, where it promotes tumor progression by deubiquitinating and stabilizing U2AF2, leading to activation of the Akt/mTOR signaling pathway. This activation induces the Warburg effect, a metabolic reprogramming characterized by enhanced glycolysis despite oxygen availability, resulting in increased glucose uptake and lactate production [142]. Consequently, OTUB2 promotes NSCLC cell growth and invasion [38]. In gastric cancer, OTUB2 and KRT80 are significantly co-overexpressed and display strong positive correlation at the protein level. Mechanistically, OTUB2 stabilizes KRT80 to activate the Akt signaling pathway, thereby enhancing gastric cancer cell proliferation [143]. OTUB2 also plays oncogenic roles in multiple other malignancies, including endometrial, cervical, thyroid, and esophageal squamous cell carcinomas (ESCCs). In endometrial cancer, OTUB2 promotes tumor proliferation and invasion by stabilizing PKM2, which activates the PI3K/Akt signaling pathway [43]. In cervical cancer, OTUB2 exerts oncogenic activity via activation of the Akt/mTOR pathway, a process driven by RBM15-mediated m6A modification that upregulates OTUB2 expression [144]. OTUD1 is associated with poor prognosis in patients with clear cell renal cell carcinoma (ccRCC). Functionally, OTUD1 deubiquitinates and stabilizes PTEN, thereby suppressing tumor growth through inhibition of the PI3K/Akt and TNF-α/NF-κB signaling pathways [145]. Similarly, OTUD3 removes Lys6-, Lys11-, Lys27-, and Lys48-linked ubiquitin chains from PTEN, thereby stabilizing it and inhibiting breast cancer cell proliferation and metastasis. OTUD3 regulates Akt signaling in a PTEN-dependent manner, and transgenic mouse studies suggest a tumor-suppressive role for OTUD3 in breast cancer [146]. A20 promotes tumor proliferation and metastasis through activation of the Akt signaling pathway [103]. Conversely, in HCC, A20 exerts tumor-suppressive effects through

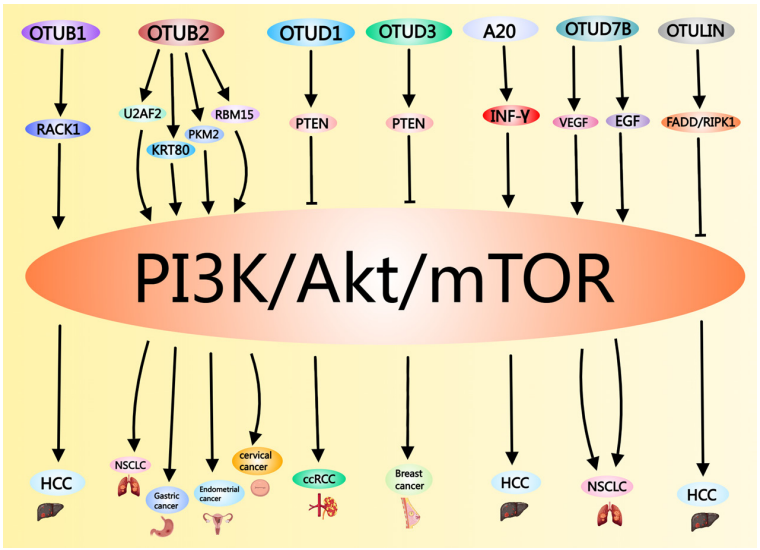


Figure 3. Regulatory mechanisms of the OTU family about PI3K/Akt/mTOR pathway.

multiple mechanisms, including enhancement of IFN-γ-mediated cytotoxicity, upregulation of anti-apoptotic Bcl-2 expression via PI3K/Akt signaling, and simultaneous promotion of STAT1 activation [147]. OTUD7B, another A20 family member, facilitates NSCLC progression by enhancing EGF-induced Akt activation. OTUD7B expression correlates positively with VEGF levels in NSCLC, implicating it in tumor angiogenesis, though the precise underlying mechanism remains unclear [148]. Furthermore, OTUD7B drives prostate cancer proliferation through activation of the Akt/mTOR signaling axis [149]. OTULIN serves as a key hepatic safeguard by maintaining M1-linked ubiquitin chain homeostasis and modulating mTOR signaling, thereby providing dual protection against hepatocyte death, inflammation, and malignant transformation [150]. In genetically engineered mouse models, OTULIN deficiency induces spontaneous hepatocyte apoptosis, hepatic inflammation, fibrosis, and ultimately HCC. Mechanistically, OTULIN preserves hepatic homeostasis by regulating the FADD/RIPK1-dependent apoptotic pathway. Loss of OTULIN disrupts the delicate balance between apoptosis and proliferation, fostering a pro-tumorigenic microenvironment that drives the pathological continuum from chronic inflammation to fibrotic remodeling and malignant transformation [151] (**Figure 3**) (**Table 1**).

EMT

Epithelial-Mesenchymal Transition (EMT) is a dynamic process that reflects the diversity and flexible changes of cell phenotypes. During this process, epithelial cells undergo phenotypic transformation into cells with mesenchymal characteristics, which is accompanied by reduced intercellular adhesion, increased motility and invasiveness, enhanced resistance to cell death, as well as strengthened apical-basal polarity and extracellular matrix (ECM)-producing capacity [152]. During embryonic development and under certain pathological conditions (including cancer and fibrosis), cells receive relevant signals (e.g., TGFβ) from the microenvironment to trigger the epithelial-mesenchymal transition (EMT) [153, 154]. EMT plays a pivotal role in cancer. Dysregulation of numerous oncogenic pathways and activation of related proteins can trigger EMT, including the Wnt/β-catenin pathway, Notch pathway, as well as proteins of the Snail family, Zeb family, and Twist family [155].

OTUB1 is overexpressed in CRC and promotes cancer cell migration and invasion by regulating EMT [156]. This process is mediated through OTUB1's deubiquitination of β-catenin protein, which enhances the expression of EMT-related genes [157]. In esophageal squamous cell carcinoma (ESCC), OTUB1 facilitates tumor progression and metastasis through deubiquitination-mediated stabilization of the EMT regulator Snail [158]. In triple-negative breast cancer (TNBC), A20 directly interacts with Snail1 and stabilizes it through monoubiquitination. Furthermore, A20 suppresses GSK3β-mediated phosphorylation of Snail1, thereby enhancing Snail1-driven epithelial-mesenchymal transition (EMT). This A20-Snail1 regulatory axis ultimately promotes tumor cell invasion and metastasis, highlighting A20 as a critical facilitator of TNBC aggressiveness [102]. A20 further enhances metastatic potential by activating

Table 1. Targets and expression of OTU family about PI3K/Akt/mTOR pathway

DUBs	Target	Effect	References
OTUB1	RACK1	Promoting HCC cell proliferation and metastasis	[24]
OTUB2	U2AF2	Activating the Warburg effect to promote NSCLC cell growth	[142]
OTUB2	KRT80	Promoting Gastric cancer cell proliferation	[143]
OTUB2	PKM2	Promoting endometrial cancer cell proliferation and invasion	[43]
OTUB2	RBM15	Promoting cervical cancer progression	[144]
OTUD1	PTEN	Inhibiting ccRCC cell growth	[145]
OTUD3	PTEN	Inhibiting breast cancer cells proliferation and metastasis	[206]
A20	IFN-γ	Enhancing cytotoxicity against HCC cells	[147]
OTUD7B	VEGF	Promoting NSCLC cell growth	[148]
OTUD7B	EGF	Promoting NSCLC progression	[148]
OTULIN	FADD/RIPK1	Maintaining hepatic homeostasis	[150, 151]

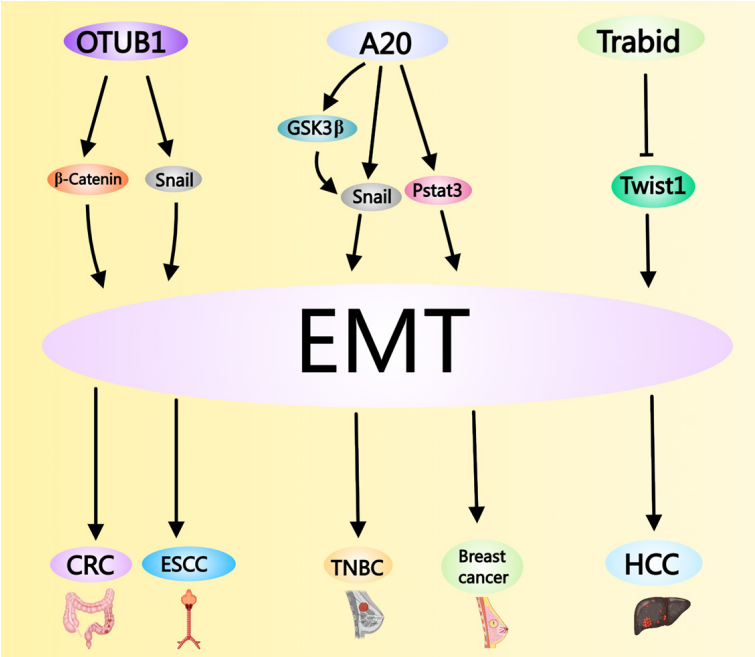


Figure 4. Regulatory mechanisms of the OTU family about EMT.

pStat3-driven signaling to reinforce a robust EMT phenotype. Notably, in murine models, A20 overexpression facilitates tumor progression by recruiting granulocytic myeloid-derived suppressor cells (MDSCs), thereby fostering an immunosuppressive tumor microenvironment [159]. The role of Trabid in hepatocellular carcinoma (HCC) remains controversial. On one hand, Trabid targets the SP1-LOXL2 axis and DDB2 through its deubiquitinating activity, thereby promoting the proliferation and invasion of HCC [124, 160]. On the other hand, Trabid binds to Twist1 and cleaves the RNF8-mediated K63-linked ubiquitin chains. Meanwhile, it facilitates the K48-linked ubiquitination of Twist1 by β-TrCP1, leading to the proteasomal degradation of Twist1. This process inhibits the Twist1-mediated epithelial-mesenchymal transition (EMT) as well as tumor invasion and metastasis in HCC cells [125] (**Figure 4**) (**Table 2**).

Wnt/β-catenin pathway

The Wnt/β-catenin pathway is an evolutionarily highly conserved signaling pathway that plays an indispensable role in numerous physiological processes, including proliferation, differentiation, apoptosis, migration, invasion, and tissue homeostasis [161]. Dysregulation of this pathway is closely associated with the occurrence, progression, and deterioration of cancer [162]. Furthermore, the Wnt/β-catenin pathway transduces signals to coordinate multiple cellular signaling cascades, including the EGFR, NF-κB, Hippo/YAP, Notch, and PI3K/Akt pathways. All these pathways play significant roles in cancer development [163-165].

In colorectal cancer, OTUB1 exerts its oncogenic effect by mediating the deubiquitination of β-catenin [157]. Similar to OTUB1, OTUB2 also binds to β-catenin and inhibits its ubiquitination, thereby activating the Wnt signaling pathway to promote CRC growth and progression

Table 2. Targets and expression of OTU family about EMT

DUBs	Target	Effect	References
OTUB1	β-catenin	EMT, Promoting CRC cell migration and invasion	[156, 157]
OTUB1	Snail	Promoting ESCC cell progression and metastasis	[158]
A20	GSK3β	EMT, Promoting TNBC cell invasion and metastasis	[102]
A20	Snail	EMT, Promoting TNBC cell invasion and metastasis	[102]
A20	PStat3	EMT, Promoting the metastatic potential of breast cancer cells	[159]
Trabid	Twist1	Inhibiting EMT and HCC cell invasion and metastasis	[125]

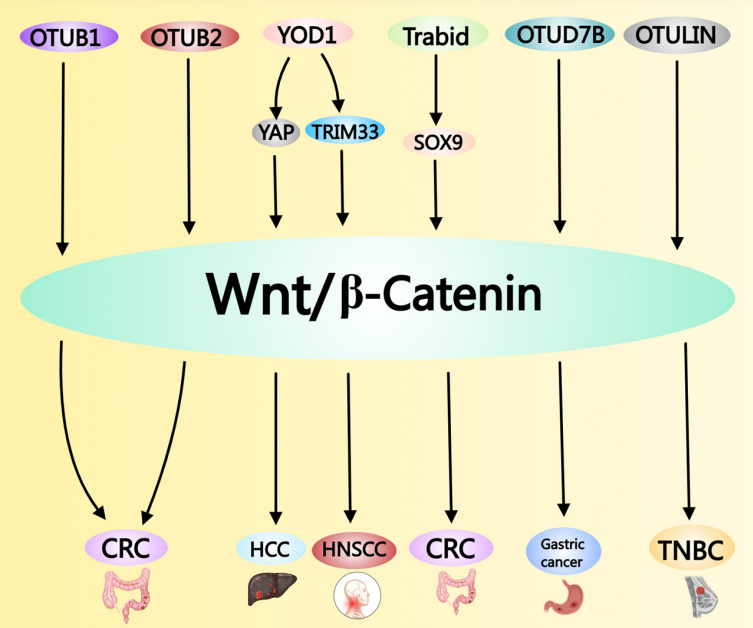


Figure 5. Regulatory mechanisms of the OTU family about Wnt/β-catenin pathway.

[166]. Furthermore, recent studies have revealed that miR-21-5p carried by the M2 macrophage derivative EV targets YOD1 and activates the YAP/β-catenin pathway to promote CD8 T-cell depletion in HCC and lead to malignant progression of primary hepatocellular carcinoma (HCC) [167]. Overexpression of YOD1 can act as an oncogene in head and neck squamous cell carcinoma (HNSCC) cells by regulating the TRIM33-mediated ERK/β-catenin pathway [168]. Similar to OTUB1 and OTUB2, Trabid critically engages the Wnt/β-catenin pathway in colorectal cancer (CRC) by deubiquitinating and stabilizing Sox9, thereby amplifying Wnt-driven oncogenic signaling to accelerate CRC progression [123]. OTUD7B is significantly overexpressed in gastric cancer, where it likely promotes tumorigenesis through activation of Wnt signaling and serves as a biomarker for poor prognosis [169]. Upon DNA damage induced by genotoxic agents, DNA-PK-mediated activation of ABL1 kinase triggers OTULIN phosphorylation. This post-translational modification enhances OTULIN's ability to suppress linear ubiquitination of β-catenin, leading to its stabilization and subsequent activation of Wnt signaling. Remarkably, this molecular cascade ultimately confers chemoresistance and enhances invasive potential in TNBC cells. These findings position OTULIN as a promising therapeutic target for TNBC treatment [170] (**Figure 5**) (**Table 3**).

Hippo/YAP pathway

The Hippo pathway is a highly conserved signaling cascade composed of MST1/2 kinases and LATS1/2 kinases. Upon activation, MST1/2 phosphorylates LATS1/2, which in turn phosphorylates the transcriptional co-activators YAP and TAZ. This phosphorylation promotes the degradation of YAP and TAZ, thereby preventing their nuclear translocation. Functionally, the Hippo pathway plays a crucial role in restricting cell proliferation and maintaining organ size and tissue homeostasis. Activation of the Hippo pathway can be triggered by various stimuli, including high cell density, G protein-coupled receptor signaling, and mechanical cues [171, 172]. However, the core kinases of the Hippo pathway are frequently inhibited in many types of cancer [173]. Moreover, the Hippo pathway is regulated at multiple levels, including through post-translational modifications [174].

In addition, OUB1 facilitates gastric cancer progression by deubiquitinating and stabilizing YAP, and thus enhances Hippo/YAP oncogenic signaling [25]. Similarly, OTUB2 increases pro-

Table 3. Targets and expression of OTU family about Wnt/β-catenin pathway

DUBs	Target	Effect	References
OTUB1	β-catenin	Promoting CRC cell migration and invasion	[157]
OTUB2	β-catenin	Promoting CRC growth and progression	[166]
YOD1	YAP	Promoting malignant progression of primary hepatocellular carcinoma (HCC)	[167]
YOD1	TRIM33	Promoting HNSCC cell proliferation and migration	[202]
Trabid	SOX9	Promoting CRC progression	[123]
OTUD7B	Wnt	poor prognosis in Gastric cancer	[169]
OTULIN	β-catenin	Enhancing chemotherapy resistance and invasion of TNBC cells	[170]

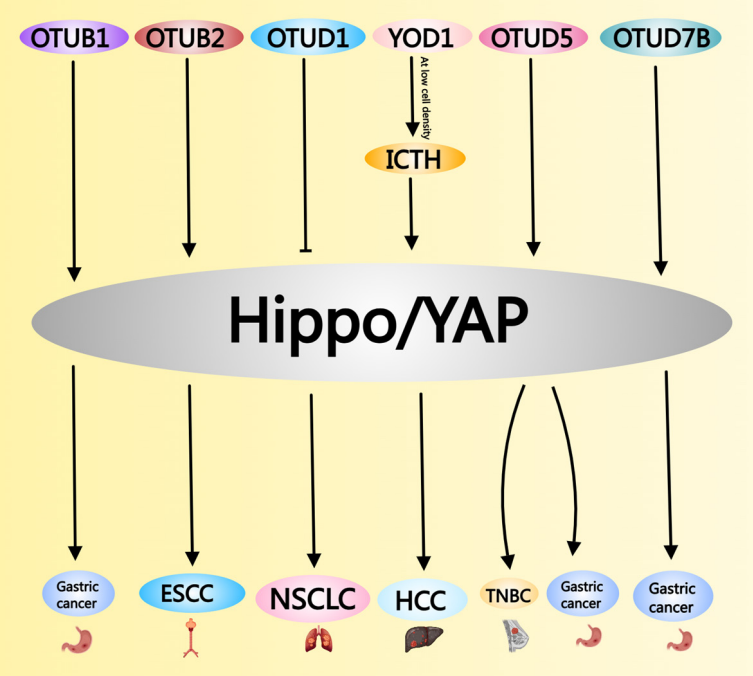


Figure 6. Regulatory mechanisms of the OTU family about Hippo/YAP pathway.

liferation and invasive ability of ESCC cells via regulation of YAP1/TAZ signaling [175]. Interestingly, it was reported that OTUD1 inhibits the nuclear translocation of YAP to suppress erlotinib resistance in NSCLC by downregulating the SOX9/SPP1 axis. This finding brings up the possibility that OTUD1 can be a double-edged sword in NSCLC [47]. Cell density is an important intrinsic regulator of the Hippo pathway. At low cell densities, YOD1 deubiquitinates and stabilizes ITCH and in particular promotes ITCH-dependent LATS degradation [176]. In a transgenic mouse model, YAP/TAZ activity-dependent overexpression of hepatic YOD1 promoted hepatocyte proliferation and hepatomegaly in response to doxycycline (Dox) induction, suggesting that YOD1 is an intrinsic positive regulator of YAP and possesses oncogenic functions in hepatocytes [176]. Conversely, at high cell densities, high expression of miR-21 reduces YOD1 levels, which stabilizes LATS and inhibits HCC progression. Thus, the endogenous YOD1-ITCH-LATS-YAP/TAZ axis is cell density dependently regulated by miR-21 [176]. In TNBC, YAP overexpression induces M2-like macrophage polarization. These YAP-overexpressing M2-like macrophages promote TNBC invasion and metastasis through the MCP-1/CCR2 axis, and OTUD5 acts as an oncogene by deubiquitinating and stabilizing YAP [177]. The classical glucose uptake inhibitor dapagliflozin, a SGLT2 inhibitor, has antitumor effects in gastric cancer by downregulating the expression of OTUD5. This inhibition increases YAP1 ubiquitination and facilitates its proteasome-dependent degradation, resulting in suppression of gastric cancer cell proliferation, migration and invasion [178]. Importantly, the combination therapy with dapagliflozin and conventional chemotherapeutic agents shows better survival advantages in xenograft mouse models, implying the possible synergism in the clinic for gastric cancer therapy [178]. However, the precise molecular mechanism underlying dapagliflozin-mediated OTUD5 regulation remains to be fully elucidated, representing an important avenue for future investigation [178]. Furthermore, OTUD7B enhances gastric cancer cell proliferation, migration, and invasion by deubiquitinating and stabilizing YAP1, thereby upregulating expression of its downstream effector NUAK2 [113] (**Figure 6**) (**Table 4**).

Table 4. Targets and expression of OTU family about Hippo/YAP pathway

DUBs	Target	Effect	References
OTUB1	YAP	Promoting Gastric cancer progression	[25]
OTUB2	YAP	Promoting ESCC cells proliferation and invasive	[175]
OTUD1	YAP	Inhibiting the resistance of NSCLC cells to erlotinib	[47]
YOD1	ICTH	Promoting HCC progression at low cell density	[176]
OTUD5	YAP	Promoting TNBC cell metastasis and invasion	[177]
OTUD5	YAP1	Promoting Gastric cancer cell proliferation, migration and invasion	[178]
OTUD7B	YAP1	Promoting Gastric cancer cell proliferation, migration, and invasion	[113]

NF-κB pathway

NF-κB is a family of structurally related transcription factors which consists of five members: RelA (p65), RelB, c-Rel, NF-κB1 (p50) and NF-κB2 (p52) [179]. The NF-κB signaling pathway is central in many physiological and pathological processes, including the regulation of the immune system, inflammation, cell proliferation and differentiation and autophagy [179-182]. It is mediated by two interlinked signaling pathways, the canonical and non-canonical NF-κB pathways. Activation of the canonical NF-κB pathway is triggered by pattern recognition receptors (PRRs) that recognise pathogen-associated molecular patterns (PAMPs). These PRRs are toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors, and nucleotide-binding oligomerization domain (NOD)-like receptors [183]. The basic mechanism is through phosphorylation and subsequent degradation of IκB proteins by IκB kinase (IKK) complex [179]. IKK can be activated by a wide variety of stimuli including cytokines, growth factors, mitogens, and microbial components [184]. In contrast, activation of the non-canonical NF-κB pathway is not dependent on I-κBα degradation, but requires proteolytic processing of the NF-κB2 precursor protein p100 into p52. This pathway is mainly activated by certain members of the tumor necrosis factor receptor (TNFR) superfamily, such as LTβR, BAFFR, CD40 and RANK [185]. Both the canonical and non-canonical NF-κB pathways are crucial for the transcriptional regulation of genes involved in immune and inflammatory responses, as well as in the regulation of cell proliferation and differentiation. Aberrant activation of the NF-κB pathway drives malignant cell growth [186] and plays a major role in the initiation and development of inflammation and inflammation-driven tumorigenesis [187].

OTUB2 is expressed at a positive correlation with p65 in HCC tissues, and OTUB2 depletion inhibits NF-κB activation through p65 phosphorylation [37]. Furthermore, overexpression of OTUB2 reverses the antitumor action of NF-κB inhibitors [37], suggesting OTUB2 as a therapeutic target for HCC intervention. OTUD1 is the DUB for FGL1 which is involved in deubiquitination and stabilization of FGL1. Studies have shown that tumor-associated macrophages (TAMs) promote the upregulation of OTUD1 expression in hepatic microenvironment by activating NF-κB signaling. This, in turn, indirectly stabilizes FGL1, thus allowing immune evasion and disease progression in patients with CRC liver metastases [188]. Interestingly, conversely to the role of A20 in normal gastric tissues, during infection with Helicobacter pylori, A20 shows tumor suppressive properties by inhibiting the activation of the NF-κB pathway and reducing the expression of related anti-apoptotic genes [189]. In B-cell malignancies, A20 also has tumor-suppressive functions and the mechanisms involved include the modulation of NF-κB signaling to promote apoptosis and inhibit tumor progression [190] (**Figure 7**) (**Table 5**).

OTU family-associated proteins in cancer

Oncogenic protein: Smoking is one of the major etiological factors in NSCLC. Studies have shown that nicotine increases OTUB1 expression, which stabilizes c-Myc by deubiquitination. This stabilization triggers c-Myc-mediated transcriptional activation of EZH2, which eventually promotes NSCLC cell proliferation and metastasis [191]. OTUB1 also specifically deubiquitinates K48 ubiquitin chains on pSTAT3-Y705, thus stabilizing and preventing degradation of pSTAT3-Y705 to promote NSCLC cell survival. Interestingly, crizotinib has been prov-

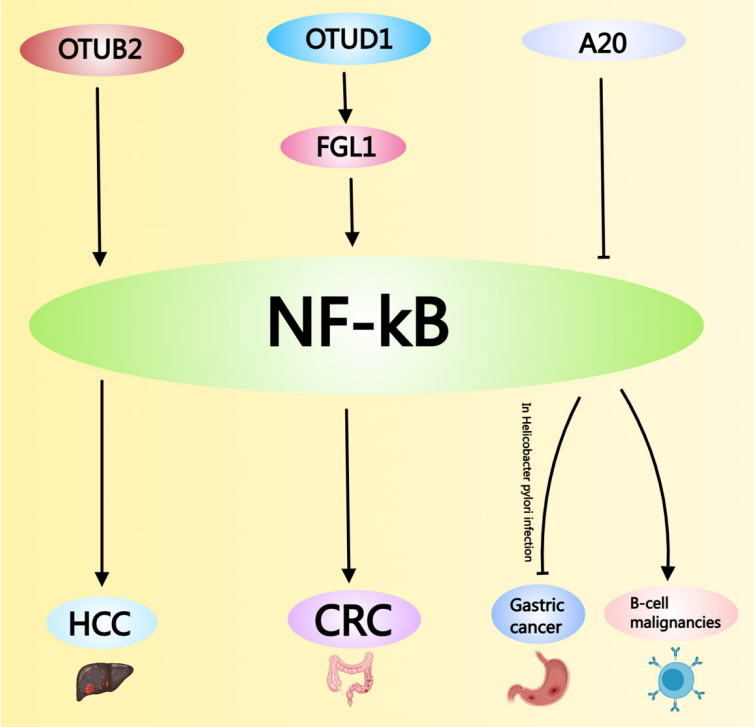


Figure 7. Regulatory mechanisms of the OTU family about NF-κB pathway.

en to block this process and inhibit NSCLC cell proliferation and colony formation. Thus, the OTUB1/pSTAT3-Y705 axis is a potential therapeutic target for NSCLC [192]. Mechanistically, OTUB1 stabilizes MYC by deubiquitinating MYC, which increases MYC-dependent transcriptional upregulation of hexokinase 2 (HK2). This metabolic reprogramming supports aerobic glycolysis and ultimately supports breast cancer progression [193]. Furthermore, OTUB1 directly interacts with and deubiquitinates the oncogenic transcription factor FOXM1, which inhibits its proteasomal degradation and substantially prolongs its protein half-life. Stabilization of FOXM1 not only increases the proliferative potential of breast cancer cells but also makes them resistant to the chemotherapeutic agent epirubicin [194]. In ovarian cancer and clear cell renal carcinoma, OTUB1 also has oncogenic effects through deubiquitinating and stabilizing FOXM1 to promote tumor cell proliferation, migration, and invasion [194, 195]. In TNBC, natural compound ailanthone (AIL) selectively inhibits the DUB activity of OTUB1 via binding to the C91 residue, which disturbs OTUB1-mediated stabilization of estrogen-related receptor α (ERRα) and induces TNBC cell death [196]. In addition, emerging data have shown the multifaceted oncogenic functions of OTUB family members in HCC. In one of the early studies, OTUB1 was found to promote HCC cell invasion and migration by modulating TGF-β signalling [197]. Furthermore, OTUB1 is also a downstream target of both miR-542-3p and circSEC24B: miR-542-3p directly targets OTUB1 to inhibit CRC progression [198], and circSEC24B mediates the interaction between OTUB1 and SRPX2 to activate downstream FAK/SRC/ERK signaling to promo te CRC progression and drug resistance [199]. In addition, OTUB1 can promote the growth of prostate cancer in vivo by activating RhoA mediating cell invasion [200], and in thyroid cancer can promote tumor cell growth by deubiquitinating and stabilizing EYA1 [201].

Similarly, in HCC, OTUB2 has tumor-promoting effects, and its overexpression promotes cell proliferation and migration by deubiquitinating PJA1 [202]. In addition, OTUB2 facilitates CRC cell proliferation and migration by inhibiting the ubiquitination of PKM2 [42]. Mechanistically, OTUB2 antagonized the interaction of PKM2 with its E3 ligase Parkin and thus prevented PKM2 ubiquitination. In line with these findings, knockdown of OTUB2 in mouse models significantly inhibits CRC growth [42].

BALF1 is an important anti-apoptotic factor in Epstein-Barr virus (EBV)-associated cancers, where it plays an important role in the regulation of apoptosis [203]. OTUD1 acts as the DUB of BALF1 and stabilizes it by deubiquitination. Interestingly, the human homolog of BALF1 is hypothesized to be a viral DUB encoded by EBV and promotes the proliferation, migration and anti-apoptotic activity of gastric cancer cells by deubiquitinating the oncoprotein Bcl-2. However, further studies are needed to confirm this proposed mechanism [204].

In particular, YOD1 was shown to specifically bind to the C-terminal ZnF structural domain of CDK1 and deubiquitinate and stabilize CDK1,

Table 5. Targets and expression of OTU family about NF-κB pathway

DUBs	Target	Effect	References
OTUB2	NF-κB and p65	Promoting HCC progression	[37]
OTUD1	FGL1	Promoting immune escape of colorectal cancer cells	[188]
A20	NF-κB	Inhibiting Gastric cancer progression in Helicobacter pylori infection	[189]
A20	NF-κB	Induce apoptosis and inhibit B-cell malignancies progression	[190]

thus promoting the growth and metastasis of TNBC [53]. As the concentration of YOD1 inhibitors or the DUB inhibitor I (G5) increases, CDK1 expression decreases, leading to reduced proliferative activity in TNBC cells [205]. Moreover, YOD1 deubiquitinates PML/RARα and its drug-resistant mutants, which increases the stability of PML/RARα protein. In contrast, YOD1 knockdown inhibits the proliferation of acute promyelocytic leukemia (APL) cells [205].

OTUD3 stabilizes GRP78 by deubiquitination and thus facilitates the proliferation and tumorigenesis of lung cancer cells in vitro and in vivo. OTUD3 is overexpressed in NSCLC and knockdown of OTUD3 leads to decreased GRP78 expression, and OTUD3 overexpression promotes tumor growth and metastasis [206]. CHIP, an E3 ubiquitin ligase for OTUD3, ubiquitinates and induces the degradation of OTUD3. Interestingly, CHIP expression is significantly decreased in human lung cancer tissues. As an important regulator in the OTUD3-GRP78 signaling axis, CHIP inhibits the expression of both OTUD3 and GRP78, and thus inhibits the invasive potential of lung cancer cells [207]. In HCC, OTUD3 drives tumor growth and metastasis in an ACTN4-dependent way, which identifies ACTN4 as a key mediator of OTUD3-induced HCC development in vivo [208]. In CRC, OTUD3 also acts as an oncogene through its interaction with a transcription factor YY1. In xenograft models, YY1 overexpression reduces the tumor growth inhibition induced by OTUD3 knockdown, and YY1 knockdown abolishes OTUD3-induced xenograft growth [209]. In CRC, YY1 expression is associated with poor prognosis and YY1 downregulates miR-500a-5p expression through binding to its promoter to promote CRC progression [209]. Moreover, phosphorylation is an important post-translational regulatory mechanism of OTUD3. Specifically, PLK1 binds to OTUD3 and phosphorylates OTUD3 at Ser326, and this promotes CRC progression by increasing OTUD3 binding and deubiquitination of YY1 [210].

OTUD4 directly binds to Snail1, causing its deubiquitination and stabilization, which promotes metastasis and invasion in TNBC [211]. Similarly, in melanoma, OTUD4 interacts with Snail1 to promote its deubiquitination and stabilization, which enhances both metastatic potential and invasive capacity. Moreover, Snail1 deubiquitination by OTUD4 is involved in Snail1-driven chemoresistance in melanoma [212]. In contrast, OTUD4 also has immunoregulatory effects by its action on CD73. Specifically, the CD73 is deubiquitinated by OTUD4, which counteracts the ubiquitination of CD73 by the E3 ubiquitin ligase TRIM21, which inhibits the cytotoxic activity of $CD8^+$ T cells and promotes tumor immune escape in TNBC. Importantly, researchers have identified a small-molecule inhibitor, ST80, which effectively disrupts the OTUD4-CD73 interaction, reactivating cytotoxic $CD8^+$ T-cell function and inhibiting the growth of immunosuppressive TNBC tumors [213]. Additionally, OTUD4 facilitates glioblastoma (GBM) proliferation and invasion by direct or indirect deubiquitinating CDK1 and activating the MAPK signaling pathway [214].

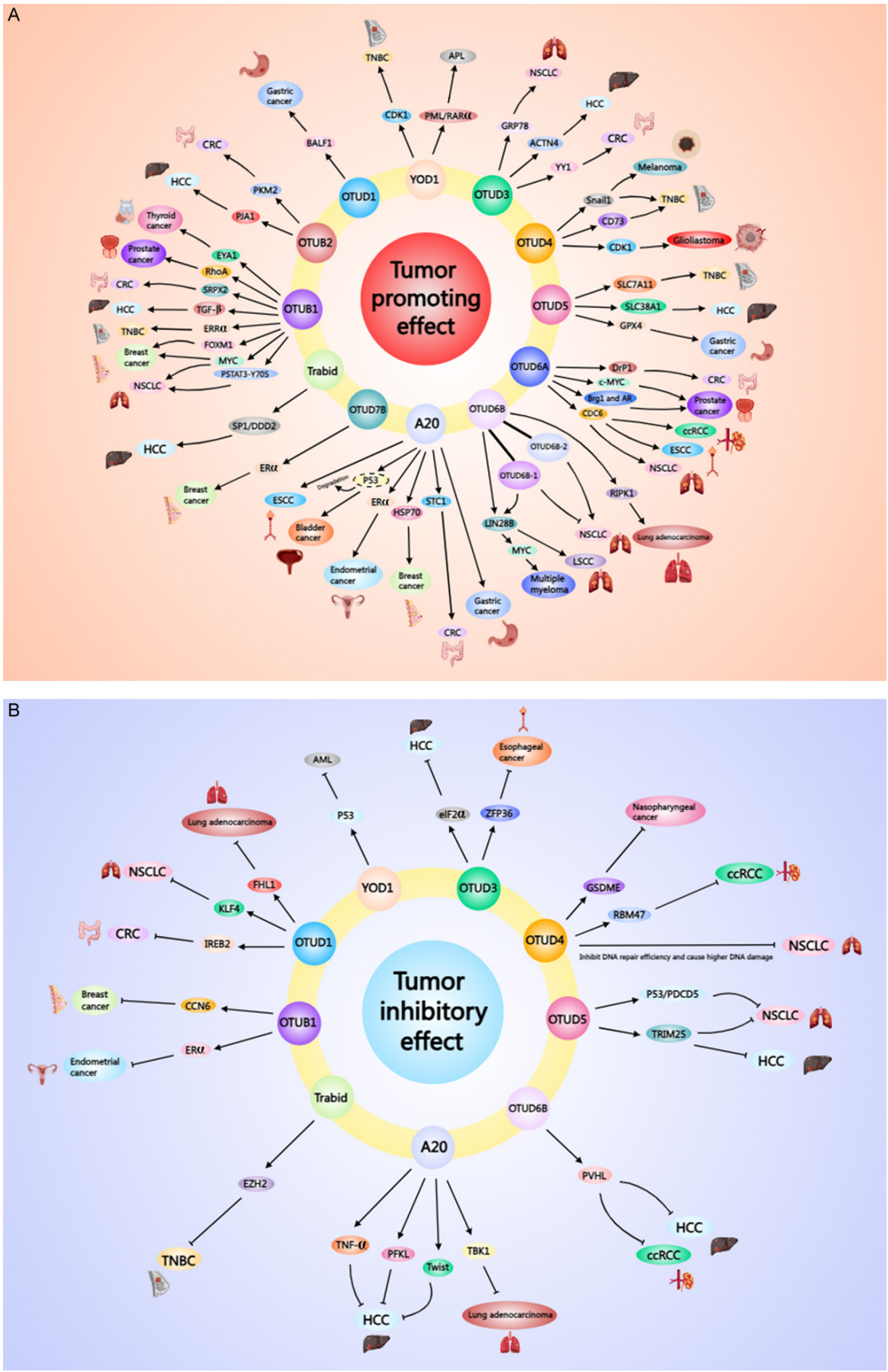
Recently, it was reported that OTUD5 has oncogenic effects through deubiquitination and stabilization of SLC7A11, thus inhibiting ferroptosis in TNBC and decreasing sensitivity to paclitaxel (PTX) [215]. Most interestingly, however, knockdown of OTUD5 significantly reduced SLC7A11 levels with no impact on GPX4 expression, which is in contrast to previous results and suggests the existence of context-dependent regulatory mechanisms for modulation of ferroptosis [75]. Moreover, SLC38A1 is highly expressed in HCC and closely associated with improved tumor growth, proliferation, invasion, and poor prognosis. OTUD5 interacts with SLC38A1, mediates its deubiquitination and increases its stability to promote HCC cell proliferation and invasion [78]. Similar to OTUB1, OTUD5 also binds to and stabilizes GPX4 to inhibit lipid peroxidation and ferroptosis to pro-

mote gastric cancer cell proliferation and tumor growth. Interestingly, the tumor suppressor p53 antagonizes this effect by binding to the OTUD5 promoter and represses its transcription, thus restoring ferroptosis sensitivity [216].

OTUD6A can deubiquitinate and stabilize Drp1 and promote its expression and increase its protein half-life, which facilitates CRC tumor growth [85]. Moreover, OTUD6A affects cellular dynamics and mitochondrial morphology; in OTUD6A-knockdown cells mitochondrial fragmentation is reduced and in HeLa cells transfected with OTUD6A shRNA mitochondria are elongated [85]. In prostate cancer, OTUD6A functions as a c-Myc-specific DUB, which deubiquitinates and stabilizes c-Myc and hence promotes tumor initiation [82]. Moreover, OTUD6A is also the specific DUB for Brg1 and AR, which removes K27-linked polyubiquitination from Brg1 and K11-linked polyubiquitination from AR, respectively, to facilitate the development of prostate cancer [83]. Through deubiquitination of CDC6, OTUD6A regulates the cell cycle and contributes to tumorigenesis in multiple malignancies, including ccRCC, ESCC and NSCLC [86]. Interestingly, isoform-specific functions of the OTUD6B DUB in cancer biology are observed. OTUD6B-1 represses protein synthesis and consequent tumor proliferation, while OTUD6B-2 promotes protein production to promote cell cycle and oncogenesis. In NSCLC cells, mRNA ratio of OTUD6B-1/OTUD6B-2 is significantly decreased compared with non-tumor tissues [87]. Furthermore, OTUD6B induces LUAD progression via deubiquitination and stabilization of RIPK1 [88]. In LSCC, MCTS1 specifically associates with the OTUD6B-1 isoform and stabilizes LIN28B, which in turn, promotes LSCC cell proliferation [90]. Likewise, OTUD6B associates with LIN28B and activates MYC during the G1/S transition of the cell cycle, which promotes the proliferation of multiple myeloma cells [89].

HSP70-mediated anti-apoptotic signaling is protective to luminal (ER^+) breast cancer cells against TNF-α-induced cell death. Intriguingly, TNFα induces the up-regulation of A20, which in turn stabilizes HSP70 by protecting it from degradation [159]. A20 is often overexpressed in CRC tissues where it choreographs an immune-evasive program through regulation of stanniocalcin-1 (STC1), a hormone-like glycoprotein. Mechanistically, A20 upregulation promotes STC1 expression which then binds to and traps calreticulin (CRT) inside mitochondria, preventing its translocation to the plasma membrane. This decrease in surface CRT leads to an impairment of APC-mediated phagocytosis of tumor cells, an inhibition of T cell activation, and ultimately a decrease in the efficacy of immune checkpoint inhibitors (ICIs) [217]. A20 overexpression therefore impairs immune-mediated tumor killing, while A20 knockdown promotes the efficacy of PD-1 blocking. Consistently, A20-deficient tumors have enhanced immune cell infiltration, and PD-1 inhibition significantly inhibits tumor progression and enhances survival in murine models [217]. Therefore, A20 is a promising predictive biomarker for ICI responsiveness in CRC patients and targeting the A20/STC1 axis may offer an effective strategy to overcome tumor immune evasion by combinatorial immunotherapy. The functional role of A20 in gastric cancer is currently being actively studied. Although A20 is always overexpressed, the mechanistic contributions of A20 are controversial [218]. Enhanced expression of NRN1 and A20 due to promoter hypomethylation has been linked to gastric cancer aggressiveness and poor clinical outcomes [219]. In contrast, during Helicobacter pylori infection, A20 has a tumor-suppressive function [189]. A20 expression is also positively correlated with poor prognosis in esophageal cancer [220]. In ESCC, A20 is highly expressed, which promotes malignant cell behavior and may be a prognostic marker and a possible therapeutic target [221]. In the case of endometrial cancer, $CD163^+$ macrophages are the predominant subtype of macrophage in lesions. These cells release cytokines like IL-1α, IL-17 alpha and TNF-α which increases A20 expression and deubiquitinates estrogen receptor α (ERα). This process induces an increase in estrogen sensitivity, proliferation and inhibition of apoptosis in endometrial cancer cells [222]. Moreover, high A20 expression is one of the contributors to therapeutic resistance in adrenocortical carcinoma [223]. Additionally, A20 can bind and inhibit the expression of p53, thus promoting the progression of bladder cancer [224].

Intriguingly, OTUD7B deficiency not only leads to the abolition of the periodic oscillation of LSD1 during cell cycle progression that results in G1 phase arrest, but also induces the in-


A
Tumor promoting effect
YOD1
OTUD1
OTUD3
OTUD4
OTUD5
OTUD6A
OTUD6B
OTUD6B-1
OTUD6B-2
OTUB1
OTUB2
Trabid
OTUD7B
A20
TNBC
APL
CDK1
PML/RARα
NSCLC
HCC
GRP78
ACTN4
YY1
CRC
Melanoma
Snail1
TNBC
CD73
CDK1
Glioliastoma
SLC7A11
TNBC
SLC38A1
HCC
GPX4
Gastric cancer
DrP1
c-MYC
Brg1 and AR
CDC6
CRC
Prostate cancer
ccRCC
ESCC
NSCLC
RIPK1
Lung adenocarcinoma
NSCLC
LIN28B
MYC
LSCC
Multiple myeloma
Gastric cancer
CRC
Endometrial cancer
Breast cancer
Bladder cancer
ESCC
Degradation
P53
ERα
HSP70
STC1
Breast cancer
ERα
HCC
SP1/DDD2
Gastric cancer
BALF1
CRC
PKM2
HCC
PJA1
Thyroid cancer
Prostate cancer
EYA1
RhoA
SRPX2
CRC
HCC
TGF-β
TNBC
ERRα
FOXM1
Breast cancer
MYC
NSCLC
PSTAT3-Y705
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Tumor inhibitory effect
YOD1
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OTUD3
OTUD4
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OTUD6B
OTUB1
Trabid
A20
AML
P53
HCC
eIF2α
Esophageal cancer
ZFP36
Lung adenocarcinoma
NSCLC
FHL1
KLF4
CRC
IREB2
Nasopharyngeal cancer
GSDME
RBM47
ccRCC
NSCLC
Inhibit DNA repair efficiency and cause higher DNA damage
P53/PDCD5
NSCLC
TRIM25
HCC
PVHL
HCC
ccRCC
Breast cancer
CCN6
ERα
Endometrial cancer
EZH2
TNBC
TNF-α
PFKL
Twist
TBK1
HCC
Lung adenocarcinoma

Figure 8. Members of the OTU family interact with related proteins to exert Oncogenic or tumor-suppressive effects.

crease of global H3K4 and H3K9 methylation levels. These epigenetic changes lead to transcriptional silencing of important regulatory genes such as cell cycle mediators (Cyclin D1, CDK6) and pro-metastatic factors (Snail), thus identifying OTUD7B as a key regulator of both proliferative and metastatic programs in breast cancer [225]. Through these mechanisms, OTUD7B is an oncogenic driver that significantly promotes breast cancer metastasis *in vivo*. Notably, OTUD7B also binds to ERa, deubiquitinates and stabilizes it, further promoting breast cancer cell proliferation and migration [115]. In addition, OTUD7B facilitates pancreatic cancer progression by regulating the Notch signaling pathway [114]. In HCC Trabid (aka ZRANB1) displays context dependent functions. On one hand, it is a tumor promoting factor that induces tumor proliferation and invasion by deubiquitinating the SP1-LOXL2 axis and stabilizing DDB2 [124, 160] (**Figure 8A**) (**Table 6**).

Tumor suppressor protein: Intriguingly, conversely to its well-established oncogenic activities, OTUB1 also displays tumor suppressor activity via a non-canonical mechanism, i.e., by inhibiting the ubiquitination of CCN6, which restrains breast cancer proliferation and metastasis [226]. Similarly, in endometrial cancer, OTUB1 plays a tumor-suppressive role in an unexpected manner by deubiquitinating and stabilizing ERα, further highlighting its context-dependent functional duality in cancer progression [227].

One of the important DUBs of FHL1, OTUD1, deubiquitinates FHL1 and inhibits the proliferation and migration of LUAD cells [228]. VE-822, a tumor suppressor that is currently in clinical trials for a variety of cancers, was found to upregulate OTUD1 expression indirectly inhibiting LUAD progression [228]. KLF4, an important member of the KLF transcription factor family, has diverse functions in cancer progression [229]. OTUD1 is a specific KLF4 DUB, which deubiquitinates and stabilizes KLF4 to inhibit the proliferation, migration, and invasion of NSCLC cells [230]. We show that knockdown of OTUD1 enhances tumor growth and reduces $CD8^+$ T cell infiltration in the TME of CRC mouse models. Mechanistically, OTUD1 binds to iron-responsive element-binding protein 2 (IREB2) and inhibits its ubiquitination, thereby stabilizing IREB2. This stabilization boosts expression of the iron transporter TFRC, leading to increased cellular iron uptake, which in turn promotes the accumulation of reactive oxygen species (ROS) and ferroptosis and simultaneously recruits $CD8^+$ T cells to enhance antitumor immunity. Taken together, these results define OTUD1 as a key regulator of tumor immunity and highlight a new therapeutic target for CRC treatment [46].

FLT3 inhibitors are very effective in the treatment of acute myeloid leukemia (AML); however, the emergence of resistance to the drug is a significant clinical problem. Stabilization of P53 has been shown to increase therapeutic efficacy [231-233]. Of particular note, the antitumor effects of FLT3 inhibitors are significantly augmented by YOD1 overexpression, which sensitizes AML cells to the actions of these agents, including drug resistance [234].

Mechanistically, OTUD3 directly interact and deubiquitinate eIF2α, thereby reducing its phosphorylation by the kinase EIF2AK3. This regulatory axis inhibits the integrated stress response (ISR) signaling pathway, which in turn sensitizes HCC cells to treatment with sorafenib. These findings make OTUD3 a potential therapeutic target for overcoming sorafenib resistance in HCC patients [235]. In addition, nicotine-mediated downregulation of OTUD3 stimulates protein degradation of ZFP36 and inhibits the decay of the messenger RNA (mRNA) of vascular endothelial growth factor C (VEGF-C), thus promoting tumor-induced lymphangiogenesis and lymphatic metastasis in esophageal cancer [236].

High promoter methylation decreases OTUD4 expression and is associated with a poor prognosis in NSCLC. Overexpression of OTUD4 sensitizes NSCLC cells to ionizing radiation (IR)-induced G2/M cell cycle arrest and apoptosis. In A549 and H460 NSCLC cells expressing an overabundance of OTUD4, OTUD4 represses DNA repair potency and raises DNA damage, thus repressing NSCLC advancement [237]. As a potent DUB of GSDME, OTUD4 promotes pyroptosis and enhances the radiosensitivity of nasopharyngeal carcinoma (NPC) cells by deu-

Table 6. Tumor-promoting effects in OTU family

DUBs	Target	Effect	References
OTUB1	c-Myc	Promoting NSCLC cell proliferation and metastasis	[191]
OTUB1	PSTAT3-Y705	Increased NSCLC cell survival rate	[192]
OTUB1	Myc	Promoting breast cancer cell growth	[193]
OTUB1	FOXM1	Promoting breast cancer cell proliferation and resistance to epirubicin	[194]
OTUB1	ERRα	Promoting TNBC cancer cell growth	[196]
OTUB1	TGF-β	Promoting HCC cell invasion and migration	[197]
OTUB1	SRPX2	Promoting CRC progression and drug resistance	[199]
OTUB1	RhoA	Promoting prostate cancer growth	[200]
OTUB1	EYA1	Promoting thyroid cancer growth	[201]
OTUB2	PJA1	Promoting HCC cell proliferation and migration	[202]
OTUB2	PKM2	Promoting CRC cell proliferation and migration	[42]
OTUD1	BALF1	Promoting Gastric cancer cell proliferation, migration, and anti-apoptosis	[204]
YOD1	CDK1	Promoting TNBC cell growth and metastasis	[53]
YOD1	PML/RARα	Enhancing APL cells progression	[205]
OTUD3	GRP78	Promoting NSCLC cell growth and metastasis	[206]
OTUD3	ACTN4	Promoting HCC cell proliferation and metastasis	[208]
OTUD3	YY1	Promoting CRC progression	[209]
OTUD4	Snail1	Promoting TNBC and melanoma cell metastasis and invasion	[211, 212]
OTUD4	CD73	Promoting TNBC immune escape	[213]
OTUD4	CDK1	Promoting glioblastoma proliferation and invasion	[214]
OTUD5	SLC7A11	Inhibiting ferroptosis in TNBC cells	[215]
OTUD5	SLC38A1	Promoting HCC cell proliferation and invasion	[78]
OTUD5	GPX4	Inhibiting Gastric cancer ferroptosis	[216]
OTUD6A	Drp1	Promoting CRC cell growth	[85]
OTUD6A	c-Myc	Promoting the onset of prostate cancer	[82]
OTUD6A	Brg1 and AR	Promoting prostate cancer progression	[83]
OTUD6A	CDC6	Promoting tumorigenesis in cancers such as ccRCC, ESCC and NSCLC	[86]
OTUD6B-1	-	Inhibiting NSCLC cell proliferation	[87]
OTUD6B-2	-	Promoting NSCLC cell cycle and tumorigenesis	[87]
OTUD6B	RIPK1	Promoting lung adenocarcinoma progression	[88]
OTUD6B-1	LIN28B	Promoting LSCC cell proliferation	[90]
OTUD6B	LIN28B	Promoting the proliferation of multiple myeloma cells	[89]
A20	HSP70	Protecting luminal (ER+) breast cancer cells from TNFα-induced cell death	[159]
A20	STC1	Promoting CRC immune escape	[217]
A20	-	Enhancing Gastric cancer cell invasion	[219]
A20	-	promoting ESCC progression	[221]
A20	ERα	Promoting endometrial cancer cell proliferation and inhibiting apoptosis	[223]
A20	P53	Promoting bladder cancer progression	[224]
OTUD7B	ERα	Promoting breast cancer cell proliferation and migration	[115]
Trabid	SP1/DDD2	Promoting HCC cell proliferation and invasion	[124, 160]

biquitinating and stabilizing GSDME [238]. Furthermore, OTUD4 promotes ATF3-induced ferroptosis and inhibits ccRCC growth by deubiquitinating and stabilizing RBM47 [239].

OTUD5 regulates the stability of p53 and PDCD5 through deubiquitination [67]. Consequently, OTUD5 suppresses NSCLC proliferation and metastasis while promoting apoptosis by modulating TP53 and PDCD5. Conversely, OTUD5 knockdown enhances NSCLC resistance to cisplatin and doxorubicin [240]. Moreover, OTUD5 deubiquitinates TRIM25 and modulates its transcriptional activity. By reduc-

ing the ubiquitination level of TRIM25, OTUD5 upregulates PML expression and promotes the formation of PML nuclear bodies (PML-NBs). PML, in turn, functions as a tumor suppressor by regulating the transcriptional activity of multiple tumor-suppressive genes [66].

OTUD6B functions as a key DUB for pVHL by binding to both pVHL and the elongin B/C subunits, thereby strengthening the interaction between pVHL and the elongin B/C complex and protecting pVHL from proteasomal degradation [241]. Notably, OTUD6B stabilizes both wild-type and mutant forms of pVHL through a non-enzymatic mechanism, ultimately suppressing the migration of HCC and ccRCC cells [91, 92].

Within the A20 DUB family, reduced A20 expression remodels the TME in LUAD, leading to immune dysregulation characterized by decreased infiltration of $CD8^+$ T cells and NK cells. Loss of A20 further amplifies TBK1-mediated STAT1 phosphorylation, resulting in PD-L1 upregulation and facilitating immune evasion. Notably, this effect is reversible by blocking TBK1 or interferon-α/β receptor (IFNAR). Paradoxically, A20 deficiency also sensitizes LUAD cells to anti-PD-L1 therapy [242]. A20 is also a multifaceted tumor suppressor in HCC. Its earliest known function is the inhibition of Twist expression, which leads to inhibition of tumor progression and metastasis [243]. In addition to its anti-metastatic activity, A20 is critical for hepatic homeostasis and the prevention of progression from chronic inflammation to malignancy. Supporting this, A20-deficient mice develop chronic hepatitis, fibrosis and finally HCC [244]. Mechanistically, A20 targets the key glycolytic enzyme PFKL for degradation and inhibits glycolysis and tumor progression in HCC [245]. Additionally, by downregulating TNF-α, A20 reduces the metastatic potential of HCC [246]. Furthermore, another member of the A20 family, Trabid, exerts tumor-suppressive effects in TNBC by deubiquitinating and destabilizing EZH2, ultimately inhibiting tumor growth and metastasis [122] (**Figure 8B**) (**Table 7**).

Environmentally dependent oncogene of OTU family members in cancer

Notably, most members of the OTU DUB family share a defining feature in cancer pathogenesis, their "environment-dependent" functional plasticity. The role they assume in tumor biology largely depends on the specific cellular context and the substrate proteins they interact with. For instance, OTUD1 exerts tumor-promoting effects in colorectal and gastric cancers but functions as a tumor suppressor in ccRCC and LUAD. YOD1 promotes tumorigenesis in TNBC and APL, while demonstrating tumor-suppressive functions in AML and HNSCC. In HCC, YOD1 displays a remarkable density-dependent functional switch, acting as an oncogene under low-cell-density conditions, whereas high-density conditions trigger miR-21-mediated YOD1 suppression that paradoxically facilitates HCC progression. Similarly, OTUD3 shows a clear functional dichotomy in that it stimulates tumor progression in cases of NSCL, HCC and colorectal carcinoma, but inhibits tumor development in breast and esophageal cancers. OTUD4 promotes cancer progression in melanoma, breast cancer, GBM and HCC, but exhibits tumor inhibitory activity in NPC and ccRCC. OTUD5 is also a context-dependent gene that promotes tumor growth in colorectal, bladder and breast cancer and is a tumor suppressor in NSCLC. Its role in HCC is controversial. Within the A20 subfamily, A20 exhibits a similar context-dependent behavior being an oncogene in breast cancer, colorectal carcinoma, melanoma, gastric cancer, endometrial carcinoma, and cholangiocarcinoma, whereas it is a tumor suppressor in B-cell lymphoma, HCC, and NSCLC. Its function in pancreatic cancer, however, still remains to be elucidated. Overall, family members of OTUs can act as either oncogenes or tumor suppressors depending on their substrate specificity. By deubiquitinating and stabilizing target proteins or modulating their activity, OTUs can either directly propagate the oncogenic or tumor-suppressive effect of these substrates or indirectly regulate associated signaling pathways. When the substrate is a known oncoprotein, OTUs usually deubiquitinate and stabilize the oncoprotein, enhancing oncogenic signaling.

Development of related inhibitors in the OTU family

In parallel with the studies of the biological functions of OTU family members in cancer pathogenesis, several OTU-targeting inhibitors with important therapeutic effects against the

Table 7. Tumor inhibitory effects in OTU family

DUBs	Target	Effect	References
OTUB1	CCN6	Inhibiting the proliferation and migration of breast cancer cells	[226]
OTUB1	ERα	Inhibiting endometrial cancer cell proliferation	[227]
OTUD1	FHL1	Inhibiting proliferation and migration of lung adenocarcinoma	[228]
OTUD1	KLF4	Inhibiting NSCLC cell proliferation, invasion, and migration	[230]
OTUD1	IREB2	Promoting ferroptosis and anti-tumor immunity of CRC	[46]
YOD1	P53	Enhancing sensitization of AML cells to FLT3 inhibitors and overcoming drug resistance	[234]
OTUD3	eIF2α	Reducing HCC cells' resistance to sorafenib	[235]
OTUD3	ZFP36	Inhibiting ferroptosis in Esophageal cancer cells	[236]
OTUD4	-	Inhibited DNA repair efficiency and caused higher DNA damage	[237]
OTUD4	GSDME	Enhancing Pyroptosis and radiosensitization of Nasopharyngeal carcinoma cells	[238]
OTUD4	RBM47	Promoting ATF3-induced ferroptosis to hinder ccRCC cell growth	[239]
OTUD5	P53/PDCD5	Inhibiting NSCLC cell proliferation and metastasis, and promoting apoptosis	[240]
OTUD5	TRIM25	Decreasing transcriptional activity and inhibiting HCC and NSCLC growth	[66]
OTUD6B	PVHL	Inhibiting cancer cell migration of HCC and ccRCC	[91, 92]
A20	TBK1	Inhibiting lung adenocarcinoma immune escape	[242]
A20	Twist	Inhibiting the progression and metastasis of HCC cells	[243]
A20	PFKL	Inhibiting glycolysis and HCC progression	[245]
A20	TNF-α	Inhibiting HCC cell metastasis	[259]
Trabid	EZH2	Inhibiting the growth and metastasis of TNBC cells	[122]

OTU-associated malignancies have been identified. Importantly, the dual OTUB1/USP8 inhibitor 61 inhibits NSCLC proliferation by simultaneous inhibition of both DUBs [246]. AIL, a natural compound, covalently targets the C91 residue of OTUB1 to inhibit its deubiquitinating activity and promote TNBC cell death through OTUB1-mediated ERRα stabilization [196]. Meanwhile, the optimized small molecule LN5P45 has great selectivity for OTUB2. Its binding causes monoubiquitination of OTUB2, which results in an enzymatic inactivation, and directly demonstrates post-translational regulation of OTUB2 activity [247]. In spite of the 48% sequence identity and 70% similarity between OTUB1 and OTUB2, the catalytic properties of the two enzymes are quite different. In OTUB1 the catalytic residues are spatially separated and form a compact catalytic triad (charged state: O_1U_1C) only when ubiquitin is bound. This conformational change leads to a closed water channel and a compact active state, which provides a structural framework that can be used for the design of selective inhibitors. In contrast, OTUB2 has intrinsic catalytic activity even in the absence of ubiquitin. Its catalytic residues, in the neutral form (O_2U_0N) already assume a close to active conformation that can be induced by only a slight proton transfer. Different structural approaches are suggested for the inhibition of OTUB2 since the active water channel and more open catalytic pocket suggest that inhibition of this enzyme would require different approaches [33]. These structural differences provide useful insights into the rational design of isoform-selective inhibitors of the OTU family. The ubiquitin isopeptidase inhibitor G5, a pharmacological inhibitor of YOD1, blocks YOD1-mediated deubiquitination of PML/RARα proteins, thereby suppressing the progression of APL, particularly drug-resistant APL, and also inhibits TNBC proliferation [205]. Two additional small-molecule inhibitors, OTUDin3 and Rolapitant, target OTUD3. OTUDin3 suppresses NSCLC cell growth, migration, and invasion, and induces apoptosis by inhibiting OTUD3-mediated deubiquitination of GRP78, leading to enhanced ubiquitination and degradation of GRP78 [248]. Rolapitant, on the other hand, inhibits OTUD3 activity, downregulates GRP78, and induces ER stress, thereby activating CHOP and the DR5 apoptotic signaling pathway in lung cancer cells [249]. Rupatadine also acts as a potent OTUD3 inhibitor, competitively binding to OTUD3 and attenuating its oncogenic role in diffuse large B-cell lymphoma (DLBCL) [250]. Furthermore, the AI-designed OTUD7B inhibitor 7Bi effectively suppresses OTUD7B enzymatic activity and inhibits proliferation in

both NSCLC and leukemia cell models [251]. NSC1122002, a novel inhibitor of Trabid, has been reported to suppress collagen-induced arthritis in mouse models, though its efficacy in cancer remains uncharacterized [252]. Previous studies on other DUB families have led to the development of molecularly targeted DUB inhibitors, such as the USP1 inhibitor ML323 [253] and the USP7 inhibitor P5091 [254]. However, research on small-molecule inhibitors has thus far focused primarily on the UCH and USP families, while the OTU family and its subfamilies remain largely underexplored in this regard [12, 255]. Therefore, screening and developing small-molecule inhibitors targeting the OTUD subfamily represents a promising yet challenging research direction. The major obstacle lies in the substantial functional heterogeneity and context-dependent "double-edged sword" behavior exhibited by OTUD members across tissue and tumor types. Consequently, OTUD-targeted therapy may induce unintended side effects. Furthermore, since OTUDs are involved in important physiological processes, high specificity and accurate dose control are very important to reduce toxicity and guarantee therapeutic safety in cancer therapy.

Discussion and conclusion

The multifaceted and context-dependent role of OTU family DUBs in cancer biology highlights their dual oncogenic and tumor-suppressive function, depending on cellular context, substrate specificity and the signaling networks in which they function. For example, OTUB1 facilitates NSCLC and gastric cancer progression by stabilizing oncogenic substrates, such as c-Myc and YAP, while inhibiting breast cancer through non-canonical stabilization of the tumor suppressor CCN6. This functional duality poses not only major challenges, but also unique opportunities for therapeutic intervention, since precise modulation of OTU targeting is required to avoid unintended potentiation of tumorigenic activity or off-target effects. A major translational challenge for the development of OTU-targeted therapeutics is the interaction specificity, as such enzymes modulate large ubiquitin-dependent signaling networks including NF-κB, Hippo, and mTOR. Although small-molecule inhibitors have shown promising anticancer activity, their therapeutic efficacy is dependent on achieving a delicate balance between inhibiting oncogenic OTU activity and preserving important physiological functions. For instance, inhibitors of OTUD3 (OTUDin3 and rolapitant) have been shown to potently inhibit progression of NSCLC by destabilizing GRP78, but their wider impact on metabolic and immune pathways needs to be rigorously assessed in preclinical safety studies. Moreover, more focus should be given to the isoform-specific targeting of OTU family members, an area that is still largely unexplored. In NSCLC, for example, OTUD6B-1 and OTUD6B-2 have antagonistic biological functions: OTUD6B-1 is a tumor suppressor and OTUD6B-2 is an oncogene. Thus, the development of selective inhibitors of OTUD6B-2 is a promising direction of research. By understanding isoform-specific structural differences, especially within allosteric pockets, and the development of covalent-allosteric inhibitors with improved selectivity, predictive biomarkers and precision oncology based on OTU isoform activity could be realized [256].

The immunomodulatory activities of the OTU family DUBs add an extra layer of complexity to their therapeutic targeting. OTUB1 and OTUD7B modulate PD-L1 stability and T cell activation and thus directly impact tumor immune escape. While this offers exciting possibilities for combining OTU inhibitors with immunotherapy to improve antitumor responses, the complex interdependence of OTUs and inflammatory signaling as illustrated by A20 regulation of NF-κB activity should be considered to prevent perturbations of immune homeostasis. Furthermore, several members of the OTU family regulate the activity of different subsets of immune cells in the TME, indicating that the development of inhibitors that can fine-tune the immune cell function may be a promising future therapeutic approach [257]. Given that aberrant tumor vasculature is a cause of immunosuppressive microenvironments and poor response to immune checkpoint blockade, concomitant anti-angiogenic agents with immunotherapies may have significant clinical benefit in cancers associated with OTU dysregulation [258]. In the future, understanding the structural basis of OTU-substrate interactions and applying AI-guided drug design will play an important role in designing highly specific, context-dependent inhibitors. Furthermore, clarify-

ing the spatiotemporal regulation of OTUs, such as density-dependent functional switch of YOD1 in HCC, will facilitate the development of context-adapted therapeutic strategies. In the long term, multi-omics datasets in patient-derived models will need to be integrated to systematically map OTU-regulated signaling networks in order to achieve precision therapeutics that take full advantage of the dual oncogenic and tumor suppressive nature of OTU family enzymes.

In summary, the OTU DUB family is a frontier of rapidly emerging cancer biology and therapeutic innovation. Despite ongoing challenges associated with substrate specificity, context-dependent functional diversity, and potential off-target effects, progress in the mechanistic and structural understanding of these enzymes is steadily moving them from complex regulatory molecules to actionable therapeutic targets. Continued investigation of isoform-specific functions, immune modulation and context specific signaling will be critical to the translation of these findings into clinically effective, precision-guided therapies that harness the full potential of the OTU family's dual oncogenic and tumor-suppressive potential.

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Disclosure of conflict of interest

None.

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