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Review

# Functional analysis of deubiquitylating enzymes in tumorigenesis and development

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ABSTRACT

Deubiquitylating enzymes (DUBs) are proteases that remove the ubiquitin moiety from ubiquitylated substrates to antagonize the modification mediated by E3 ubiquitin ligases. Currently, DUBs have been found to play critical roles in the regulation of various physiological or pathological processes, such as embryogenesis, immune homeostasis, tumorigenesis and neurodegenerative diseases. Accumulating evidences have suggested that different DUBs exert distinct function such as oncogenic, tumor-suppressive or context-dependent roles in tumorigenesis, mainly by affecting the protein stability, enzymatic activity or subcellular localization of its substrates. Importantly, multiple potent inhibitors targeting the enzymatic activity of oncogenic DUBs have been developed and show promising anti-cancer efficacy in preclinical models. Thus, exploring the unique role of DUB enzymes and their downstream effectors will provide novel insights into the molecular basis of cancer development. Here, we review and summarize recent progress on DUB functional annotation, as well as its biochemical regulation, to provide a better understanding for cancer therapies by targeting DUBs.

## 1. Introduction

### 1.1. General introduction of the ubiquitin-proteasome system

The ubiquitin-proteasome system (UPS) serves as an evolutionarily conserved modulator of protein homeostasis in eukaryotic organisms [1]. The entire system is primarily constituted by ubiquitin, ubiquitylation enzymes, and the 26S proteasome. The working mechanisms of the UPS has been extensively documented [2–4]. Briefly, the ATP-dependent activation of the 76-amino-acid ubiquitin protein by an E1 activating enzyme is indispensable for the initiation of the enzymatic cascades [3]. As a result of the activating reaction, conformational changes on ubiquitin expose its carboxyl group at the C-terminus. Through a trans-esterification reaction, activated ubiquitin is then transferred to an E2 conjugating enzyme by the formation of thioester bond. Functionally, E2 enzyme assists in the recruitment of activating ubiqutitin into an association with E3 ligases. E3 ligase recognizes target protiens for ubiquitination often through binding a consensus sequence which is often modified by post-translational modifications, thus marking them for ubiquitination. Thereby, E3 ligases determine substrate specificity and facilitate the formation of a covalent isopeptide bond between the carboxyl group at C-terminal of ubiquitin and lysine residues on target substrate proteins, promoting their ubiquitination. Additionally, E3 ligases may also mediate the attachment of the ubiquitin moiety to existing ubiquitin on a target protein, thereby building inter-ubiquitin chains to accommodate diverse functional outputs [5,6]. This machinery enables an intracellular cascade to sequentially tag proteins with poly-ubiquitin chains that under most circumstances results in proteolysis of targeted proteins, or with mono-ubiquitin chain that often leads to non-degradation outcomes to a protien function such as altered activity or subcellular localization [7]. Due to its central role in regulating protein homeostasis, UPS is involved in the regulation of nearly every aspect of cellular biology, especially cell growth, immune response, and metabolic homeostasis [5]. Because of its important physiological roles, dysregulation of the UPS under pathological conditions contribute to multiple human

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disorders, including but not limited to neurodegeneration, autoimmune abnormalities and tumorigenesis [8]. Ubiquitylation is a reversible process, with E3 ubiquitin ligases attaching ubiquitin to substrates and deubiquitylating enzymes removing ubiquitin from substrates. As E3 ubiquitin ligases have been extensively reviewed previously [4,9–11], here our major topic will be focused on deubiquitylation.

### 1.2. Deubiquitylating enzymes and subfamily (structures & mechanisms)

Deubiquitylating enzymes (DUBs) are proteases that cleave ubiquitin moieties from either ubiquitylated substrates or poly-ubiquitin chains [12]. Currently, around 100 DUBs have been identified in the human genome, which are categorized into six major subfamilies, including ubiquitin-specific proteases (USPs), ubiquitin C-terminal hydrolases (UCHs), ovarian tumor proteases (OTUs), motif interacting with ubiquitin-containing novel DUB family (MINDYs), Josephins (also termed MJDs) and Jad1/Pad/MPN-domain-containing metalloenzymes (JAMMs) [13–15]. USP is the largest group among all subfamilies, with 54 members encoded in the human genome [14]. As the major regulator of cellular deubiquitylating process, DUBs serve to counteract ubiquitylation and proteolysis activities and consequently maintain the homeostasis of protein quantities and activities in cells [16]. There are four major functional mechanisms adopted by DUBs in mammalian cells, including 1) processing of the ubiquitin precursor; 2) rescuing protein substrates from degradation or non-degradation activities via reversing the ubiquitylation conjugation; 3) cleaving poly-ubiquitin chains for ubiquitin recycling; and 4) editing ubiquitin chains to exchange one type of ubiquitin signal to another [17,18], which collectively and ultimately increase the free ubiquitin pool. Different subfamilies of DUBs share overlapping, as well as distinct, biochemical mechanisms, which are further discussed in subsequent chapters. All these highlight a critical role for DUBs in many important cellular functions (Fig. 1).

### 1.3. Physiological significance and pathological roles of DUBs

As key factors regulating protein homeostasis, DUBs are involved in major physiological events, such as signaling transduction (degradation of signaling intermediates, activation of kinases, protein localization, proteolysis and regulation of gene expression) and cell fate control (apoptosis, DNA repair, segregation of chromosome, cell cycle progression and spermatogenesis) [12,16,18]. All these activities can be attributed to DUBs' counteracting effects on the protein ubiquitylation system. For instance, USP44 is responsible for the deubiquitylation of CDC20 (cell-division cycle protein 20), which is a co-activator of the E3 ubiquitin ligase complex APC/C (anaphase promoting complex/cyclosome) that triggers degradation of various cell cycle regulators. Therefore, USP44 activity is essential for the regulation of the spindle checkpoint and proper execution of chromosome segregation [19].

Dysregulation of DUBs has also been linked to various human pathological conditions, such as congenital developmental defects [20], neurodegenerative diseases [21], metabolic dysregulations [22], autoimmune disorders [23] and neoplastic events [24]. For example, USP18 was found to be aberrantly downregulated in liver tissues of NAFLD mice (nonalcoholic fatty liver disease) induced by high-fat diet. USP18 deficiency leads to enhanced ubiquitylation and subsequent autophosphorylation of TAK1 (transforming growth factor β-activated kinase 1), which further activates the NF-κB signaling pathway and results in insulin resistance [22]. Moreover, loss-of-function mutations on *STAMBP* (STAM-binding protein) [25] and *UCH-L1* (UCH isozyme L1) [26] are frequently found among patients with Microcephaly-Capillary Malformation Syndrome and Parkinson's Disease, respectively, which lead to aberrant endocytosis, cytoplasmic aggregation of disease-related proteins, and neuronal apoptosis. Thus, DUB-targeted therapeutics may hold promises on treating these diseases.

### 1.4. General introduction of the molecular mechanism of DUB regulation by upstream signaling pathways, including phosphorylation, ubiquitylation and other post-translational modifications

Due to their critical roles in regulating protein homeostasis, the abundance, subcellular localization and catalytic activity of DUBs are also tightly controlled by various upstream signaling events [27]. Although protein abundance of the most DUBs is relatively low, they typically display tissue-specific expression patterns [28]. This phenomenon is likely due to the fact that DUBs are regulated by cell signaling pathways controlling their transcription, translation and degradation [14]. For example, the expression of A20, a TNF-induced DUB, could be stimulated upon NF-κB activation. Upon inhibition of the NF-κB activity, A20 is cleaved by the paracaspase MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1) to decrease its functional activity [29]. Besides caspase-involved processing, DUBs also undergo self-processing, such as USP1, which can cleave itself upon UV radiation, subsequently leading to self-degradation [30]. These findings suggest that the regulation of DUB protein abundance appears to be tissue-specific in order to accommodate different cellular situations.

In response to physiological needs, DUBs also display diverse and cell type-dependent subcellular localization [31]. The localization of DUBs is controlled by two major post-transcriptional modifications, phosphorylation and ubiquitylation. For example, phosphorylation of OTUB1 (OTU domain-containing ubiquitin aldehyde binding protein 1) by CK2 (casein kinase 2) facilitates to its nuclear entry [32], whereas USP4 is exported from the nucleus upon AKT-mediated phosphorylation [33]. On the other hand, ubiquitylation of BAP1 (BRCA1-associated protein 1) by UBE2O (ubiquitin-conjugating enzyme E2 O) inhibits its nuclear transportation, a process that can be antagonized by self-deubiquitylation [34]. Moreover, modifications such as phosphorylation, hydroxylation or auto-deubiquitylation of DUBs have also been reported to regulate their interaction with substrates, which affects their deubiquitylating activity towards downstream substrates [35–37].

Post-translational modifications are major regulatory mechanisms controlling the catalytic activity of DUBs, including phosphorylation, ubiquitylation, SUMOylation and oxidation. For instance, the catalytic activity of DUBs could be regulated by phosphorylation in both negative and positive manners, with phosphorylation sites lying outside or inside their catalytic domains [14]. Although the exact molecular mechanisms regarding how the phosphorylation of certain sites triggers catalytic alterations remain largely unclear, OTUD5 (OTU domain-containing protein 5) may serve as an example to make potential interpretations. Detailed crystal structure results demonstrate that phosphorylated OTUD5 generates a more stabilized catalytic domain and a dehydrated active site by the folded phosphorylation loop, which structurally explains why phosphorylation enhances its enzymatic activity [38]. Similar to phosphorylation, ubiquitylation of DUBs can also inhibit or enhance their catalytic efficacies. One major mechanism underlying its negative impact occurs when DUBs form a complex with E3 ligases, where the covalently-attached ubiquitin could compete with substrates to bind with DUBs. Therefore, this reduces their binding with substrates and catalytic function as well [39,40]. However, mono-ubiquitylation of ATXN3 (ataxin-3) could increase its catalytic activity in part by triggering an activating conformational alteration in an unknown mechanism [41,42]. Moreover, SUMOylation could also inhibit the activity of DUBs, for instance through the recruitment of poly-ubiquitylated substrates by USP25 and USP28, where the targeted sites of SUMOylation are inside their catalytic domains [43,44]. CYLD (cylindromatosis-associated DUB) may also be suppressed by SUMOylation with the modification site outside of its catalytic domain [45]. Since the majority of DUBs are cysteine proteases featuring reactive cysteine residues, they are relatively susceptible to oxidations. To this end, oxidation by ROS (reactive oxygen species) has been linked to the inactivation of USP and UCH subfamilies, which is a reversible process

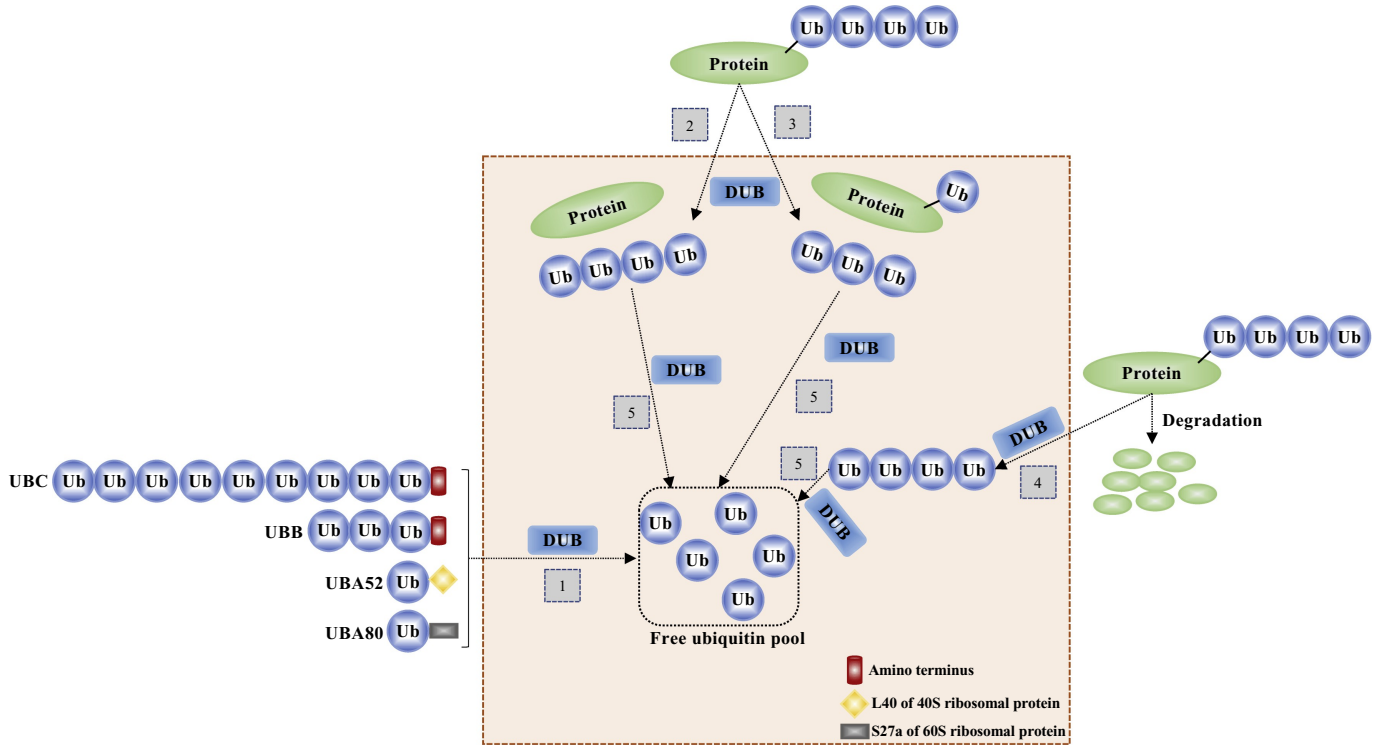


**Fig. 1.** General roles of DUBs in the regulation of ubiquitin homeostasis.
1. Precursor processing: Ubiquitin is encoded by four genes (namely UBC, UBB, UBA52 and UBA80) and translated as forms of multiple ubiquitin copies fused with either ribosomal proteins or amino terminus, which require the cleavage by DUBs in order to generate free single ubiquitin. 2. Cleavage of protein-ubiquitin interaction: DUBs help to prevent degradation or non-degradation events on targeted proteins by completely removing ubiquitin chains from substrates. 3. Editing ubiquitin-ubiquitin interaction on substrates: DUBs could also alter the functional impact of ubiquitylation on substrates by cleaving inter-ubiquitin chains (such as changing from degradative ubiquitylation to non-degradative ubiquitylation). 4. Recycling of ubiquitin: DUBs also prevent the proteasomal degradation of ubiquitin following substrate degradation. 5. Disassembly of ubiquitin chains: All ubiquitin chains could be disassembled as single ubiquitin into free recycling ubiquitin pool.

depending on ROS concentration [46–48]. Apart from post-translational modifications, substrate-assisted catalysis [49] and allosteric regulations also control the catalytic activity of DUBs [50], which appear to be relatively less significant compared to post-translational modifications in controlling DUB activity.

### 1.5. The clinical implications of DUBs with major focus on tumorigenesis

As aforementioned, dysfunctional DUBs have been linked to multiple human pathological conditions, including neoplastic disorders. DUBs are extensively involved in cell cycle regulation, DNA damage repair and cell growth control, which are all hallmarks of tumorigenesis [24]. Mechanistically, most malignancies feature overexpression of oncoproteins, which are normally degraded by proteolytic machineries. Nevertheless, when DUBs are aberrantly activated genetically or functionally, their corresponding proteolytic processes towards specific oncoprotein substrates may be at least partially diminished [51]. Therefore, proper inhibition on those aberrantly activated DUBs in cancer cells could be a novel promising anti-tumor strategy. From a pharmaceutical perspective, the design of an available and efficient inhibitor of DUBs should at least solve three major technical difficulties as follows. First, this compound should be as specific as possible since DUBs often share high level of homology in their enzymology. Most DUBs usually target multiple proteins while one specific protein could also be deubiquitylated by various DUBs. Therefore, an ideal inhibitor would target a closely related family of DUBs sharing the same substrates, which could minimize side effects while maintaining therapeutic efficacy [52]. Second, since the active domains of DUBs are highly conserved and Cys-dependent, it is hard to specifically inhibit certain types of DUBs by targeting their enzymatically active domains. A more unique target site will be necessary to reduce inhibition of irrelevant DUBs [52,53]. Third, high molecular weight molecule of DUBs may be another obstacle to prevent adequate bioavailability of DUB inhibitors even though their three-dimension structures are proposed to be qualified [53,54]. So far, several DUB inhibitors have been verified as effective in battling malignant neoplasms, especially those targeting USP1, USP7, and UPS14, which display great potential for clinical application. Details of the neoplastic role of each subfamily of DUB are specifically reviewed in the following chapters, except MINDY, which is a recently identified novel subfamily that contains only one member, MINDY-1 [55] and has not yet been linked to tumorigenesis (Fig. 2 and Fig. 3).

### 1.6. Non-canonical activities of DUBs and their functional implications

Besides their catalytic deubiquitylating activities, several non-canonical functions of DUB, such as USP18, OTUB1 and A20s, have been recently identified in regulating various physiological and neoplastic processes. Via recruiting USP20 and then facilitating USP20-STING interaction and deubiquitylation process, USP18 is found to function as a scaffolding protein to indirectly deubiquitylate STING and promote the innate antiviral responses in mouse models [56]. Additionally, several studies have demonstrated a non-catalytic deubiquitylating function of OTUB1 on certain proteins, such as p53 [57], Mdmx [58], RAS [59] and SMAD2/3 [60], which either trigger or suppress neoplastic development. Mechanistically, all these non-catalytic deubiquitylations are mediated by suppressing the activity of relevant E2 conjugating enzymes to subsequently reduce the ubiquitylation levels on corresponding E3 ubiquitin ligase substrates [61]. Furthermore, DUBs could also act as E3 ligases to induce ubiquitylation besides its

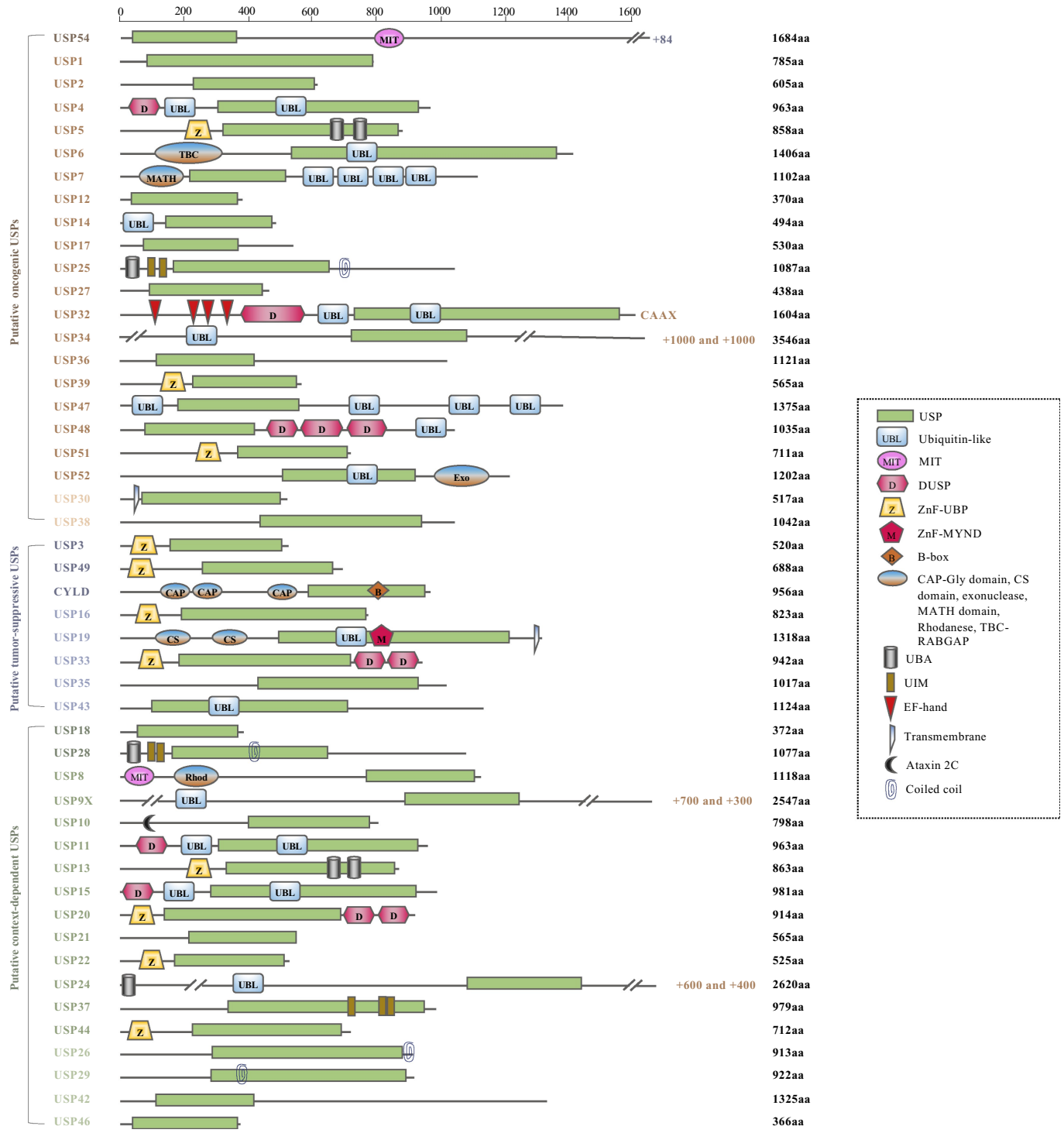


**Fig. 2.** Structural domains of major neoplastic USPs.
Note: Different shades of color under the same category indicate different evidence levels. For example, dark-blue tumor-suppressive USPs are supported by strong evidence while light-blue counterparts are backed by potential or less potential neoplastic evidence.

deubiquitylating activities, such as A20, which triggers mono- or poly-ubiquitylation of Snail1 and RIP1 and ultimately contributes to the oncogenesis of breast cancer [62] and glioblastoma [63]. However, currently there is little knowledge about cellular coordination on the two opposing enzymatic functions, which warrants further in-depth investigations.

## 2. Major functions of mammalian deubiquitylating enzymes and their substrates

### 2.1. The USP subfamily

#### 2.1.1. Introduction of USPs

Currently, USP is the largest subfamily of DUBs, with at least 54 members being reported in human species [14]. The structure of USP fold is highly conserved, mainly consisting of three subdomains.

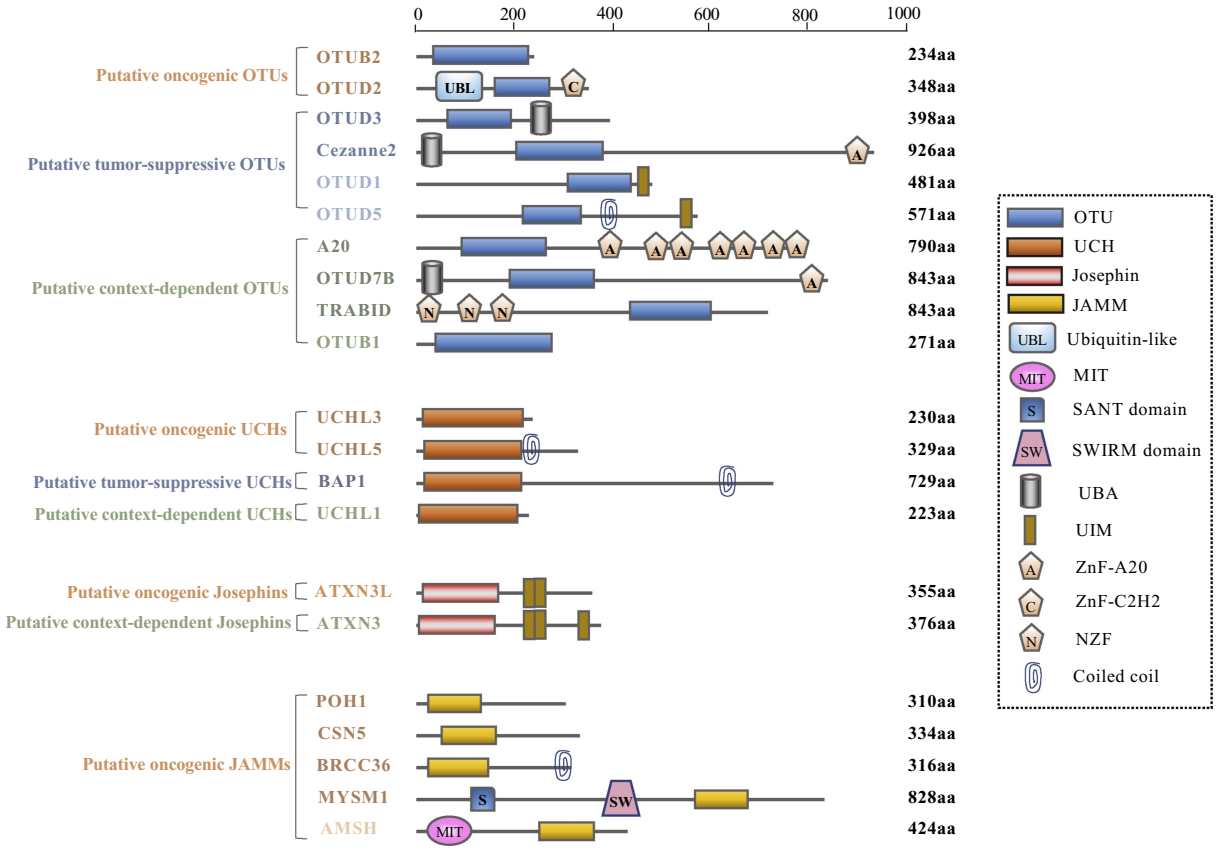


**Fig. 3.** Structural domains of major neoplastic non-USP DUBs.
Note: Different shades of color under the same category indicate different evidence levels. For example, dark-blue tumor-suppressive OTUs are supported by strong evidence while light-blue counterparts are backed by potential or less potential neoplastic evidence.

Structurally, these three subdomains resemble the palm, thumb and finger of a right hand, respectively. The catalytic core of USP lies at the interface between the palm and the thumb subdomain, while the globular portion of ubiquitin interacts with the finger subdomain [13,18]. CYLD, which lacks a finger subdomain, is an exception among all USPs [64]. Similar to the majority of DUBs, USPs regulate various physiological processes, such as DNA repair, cell cycle progression and transcriptional activities [52]. Likewise, dysfunction of USPs has also been linked to multiple pathological conditions, such as azoospermia [65], ataxia [66], Parkinson's Disease [67] and Cushing's Disease [68]. Meanwhile, owing to essential contributions in the regulation of cell cycle and DNA stability, their roles in tumorigenesis have also been extensively investigated, which are described in subsequent chapters.

### *2.1.2. Physiological roles of USPs-evidence from knockout and transgenic mouse models*

Similar to E3 ubiquitin ligases, USPs also have been linked to various physiological functions in mammals [13]. Based on evidence from knockout and transgenic mouse models, we briefly discuss the physiological roles of USPs, with respect to embryonic development and regulation of cardiovascular, hematopoietic as well as endocrine homeostasis (Table 1).

In terms of embryonic development, systemic ablation of certain USPs leads to embryonic or perinatal lethality, including *USP1* [69], *USP7* [70], *USP9X* [71], *USP10* [72], *USP14* [73,74], *USP16* [75], *USP22* [76] or *USP36* [77]. Different mechanisms have been delineated in relation to these embryonic lethalities, such as impaired skeletogenesis and hematogenesis by *Usp1* depletion [69] and widespread embryonic cell apoptosis after systematically removing *Usp22* [76], which suggest the pivotal role of these USPs in regulating differentiation and maturity of embryonic cells. Meanwhile, conditional knockout of *Usp7* [78] or *Usp9X* [79] in brain also leads to perinatal lethality, due to hypoplasia and deficiencies in brain development, especially axonogenesis.

USP4, USP15, USP18, USP20 and CYLD play a regulatory role in the cardiovascular system. USP4 [80] as well as USP18 [81] display protective effects in cardiovascular dysfunctions, since depletion of each DUBs deteriorates cardiac remodeling due to pressure overload. In addition, transgenic overexpression of *Usp20* in smooth muscle cells also results in attenuated inflammation and atherosclerosis among mouse models, indicating a protective effect by USP20 as well [82,83]. On the other hand, USP15 and CYLD appear to negatively impact on cardiac homeostasis, since transgenic *Usp15* overexpression in cardiac cells induces cardiac hypertrophy [84] and systemic depletion of *Cyld* ameliorates myocardial oxidative stress, cardiac maladaptive remodeling and heart failure after pathological pressure overload [85]. All these findings implicate the diverse roles of USPs in the regulation of cardiovascular physiology.

The physiological roles of USPs have also been extensively investigated in the hematopoietic and immune systems. Deletion of *Usp1* and *Usp3* result in phenotypes of Fanconi anemia [86] and age-dependent lymphopenia respectively [87]. Moreover, systemic deficiency of *Usp16*, *Usp18* or *Cyld* is also linked to defective development of bone marrow progenitor cells [75], dendritic cells [88] and T cells [89] respectively, culminating in abnormal hematopoiesis among mouse models. In terms of immune regulation, USPs seem to play context-dependent roles by activating or inhibiting the immune responses. Specifically, genetic ablation of *Usp15* [90], *Usp21* [91] or *Usp38* [92] leads to enhanced anti-viral responses and T-cell activation. Likewise, conditional deletion of *Usp9X* in T-cells induces spontaneous lupus-like

**Table 1**
Major phenotypes of USPs knockout and transgenic mice.

| Gene | Mode | Phenotypic alterations | |
|---|---|---|---|
| | | Cancer-relevant | Cancer-irrelevant |
| *Usp1*$^{-/-}$ | Systemic | NA | **Embryogenic:** Perinatal lethality with abnormal skeletogenesis, growth retardation, male infertility and Fanconi anemia [69,86] |
| *Usp2*$^{-/-}$ | Systemic | NA | **Nervous:** Dysregulated behavioral circadian rhythms [487,488]<br>**Digestive:** Hyperabsorption of dietary calcium in small intestine [489]<br>**Reproductive:** Male infertility with defects in fertilization and sperm motility [104,490] |
| *Usp2* (transgenic) | Conditional (macrophage) | NA | **Endocrinal:** Resistant to high-fat diet-induced obesity and retarded progression of insulin resistance [100] |
| *Usp3*$^{-/-}$ | Systemic | **Unspecified:** 1. Increased incidences of tumorigenesis [87] | **Hematopoietic:** Shortened lifespan and age-dependent lymphopenia [87] |
| *Usp4*$^{-/-}$ | Systemic | NA | **Immune:** More sensitive to radiation-induced apoptosis in both thymus and spleen [491]<br>**Cardiovascular:** Severer pressure overload-induced heart enlargement and cardiac dysfunction [80] |
| | Conditional (liver) | NA | **Endocrinal:** Deteriorated insulin resistance and obesity induced by high-fat diet [96] |
| *Usp4* (transgenic) | Conditional (heart) | NA | **Cardiovascular:** Ameliorated pathological cardiac hypertrophy due to pressure overload [80] |
| | Conditional (liver) | NA | **Endocrinal:** Ameliorated insulin resistance and obesity induced by high-fat diet [96] |
| *Usp7*$^{-/-}$ | Systemic | NA | **Embryogenic:** Embryonic lethality [70] |
| | Conditional (brain) | NA | **Nervous:** Neonatal lethality due to developmental hypoplasia and deficiencies in brain [78] |
| *Usp8*$^{-/-}$ | Conditional (T-cell) | NA | **Immune:** Lethal colitis [492] |
| *Usp9x*$^{-/-}$ | Systemic | NA | **Embryogenic:** Embryonic lethality [71] |
| | Conditional (dorsal telencephalon) | NA | **Nervous:** Dramatic decrease in hippocampal size [79] |
| | Conditional (germ cell) | NA | **Reproductive:** Aberrant spermatogenesis and complete infertility [106] |
| | Conditional (gut) | **Colorectal cancer:** Increased tumor burden in colitis-associated colorectal cancer [195] | **Digestive:** Reduced body weight due to impaired intestinal regeneration during acute colitis [195] |
| | Conditional (T-cell) | NA | **Immune:** Spontaneous lupus-like autoimmunity and lymphoproliferative disease [71] |
| | Conditional (neural progenitor) | NA | **Embryogenic:** Perinatal lethality with disrupted axonogenesis [79] |
| *Usp10*$^{-/-}$ | Systemic | NA | **Hematopoietic:** Neonatal lethality with bone marrow failure and severe anemia [72] |
| | Conditional (liver) | NA | **Digestive:** Deteriorated hepatic steatosis and insulin resistance induced by high-fat diet [97] |
| | Conditional (endothelium) | NA | **Angiogenesis** increased vessel sprouting during angiogenesis [493] |
| *Usp10* (transgenic) | Conditional (liver) | NA | **Digestive:** Alleviated hepatic steatosis and insulin resistance induced by high-fat diet [97] |
| *Usp13*$^{-/-}$ | Systemic | NA | **Immune:** More resistant to viral infection [494] |
| *Usp14*$^{-/-}$ | Systemic | NA | **Nervous:** Resting tremor, a reduction in muscle mass, notable hindlimb rigidity and postnatal lethality among ataxia mice [73,74] |
| *Usp14* (transgenic) | Conditional (brain) | NA | **Nervous:** Restored viability and motor function, as well as preventing postnatal lethality among ataxia mice [107,108] |
| *Usp15*$^{-/-}$ | Systemic | **Sarcoma:** Hypersensitive to methylcholantrene-induced fibrosarcoma [495] | **Immune:** Enhanced T-cell activation by stimulation [90] |
| *Usp15* (transgenic) | Conditional (heart) | NA | **Cardiovascular:** Cardiac hypertrophy [84] |
| *Usp16*$^{-/-}$ | Systemic | NA | **Embryogenic:** Early embryonic lethality [496] |
| | Conditional (bone marrow) | NA | **Hematopoietic:** Huge reduction of mature and progenitor cell populations and causing lethality [75] |
| *Usp18*$^{-/-}$ | Systemic | **Breast cancer:** Reduction of mammary tumor growth [227]<br>**Lung cancer:** Reduced tumorigenicity of Kras-driven lung cancers [228]<br>**Sarcoma:** Spontaneous development of leiomyosarcoma [230] | **Immune:** Impaired generation of dendritic cells from bone marrow [88]; More susceptible to HSV-1 infection [56]; Decreased immune reactions towards choriomeningitis and myeloencephalitis induced by choriomeningitis virus or vesicular stomatitis virus respectively [497]; Lower incidences of autoimmune diabetes [93]; Resistant to experimental autoimmune encephalomyelitis [94]<br>**Cardiovascular:** Deteriorated cardiac remodeling due to pressure overload [81]<br>**Digestive:** Gaining more liver weight after high-fat diet [498]<br>**Osteogenic:** Osteopenia [499] |
| *Usp18*$^{-/-}$ | Conditional (bone marrow) | **Leukemia:** Resistant to BCR-ABL–induced chronic myeloid leukemia [229] | NA |
| *Usp18* (transgenic) | Conditional (heart) | NA | **Cardiovascular:** Alleviated cardiac remodeling due to pressure overload [81] |
| | Conditional (liver) | NA | **Digestive:** Gaining less liver weight after high-fat diet [498] |

(*continued on next page*)

**Table 1** (*continued*)

| Gene | Mode | Phenotypic alterations | |
|---|---|---|---|
| | | Cancer-relevant | Cancer-irrelevant |
| *Usp19*$^{-/-}$ | Systemic | NA | **Endocrinal:** Enhanced muscle regeneration following cardiotoxin-induced muscle injury [500]; Losing less muscle mass, retaining more strength and having less myofiber atrophy in response to glucocorticoids [101,102]; Smaller fat pads, higher percentage of lean mass and better insulin sensitivity induced by high-fat diet [103] |
| *Usp20* (transgenic) | Conditional (smooth muscle cell) | NA | **Cardiovascular:** Attenuated inflammation and atherosclerosis [82,83] |
| *Usp21*$^{-/-}$ | Systemic | NA | **Immune:** Splenomegaly and more resistant to viral infection [501]; Spontaneous T-cell activation [91] |
| | Conditional (embryonic stem cell) | NA | **Embryogenic:** Loss of morphology and self-renewal among embryonic stem cells [502] |
| | Conditional (Treg cell) | NA | **Immune:** Immune disorders with lymphadenopathy, splenomegaly and increased lymphocytic infiltration into peripheral organs [503] |
| *Usp22*$^{-/-}$ | Systemic | **Leukemia:** Early neonatal lethality with smaller body sizes and spontaneous generation of acute myeloid leukemia among Kras-activated mice [253] | **Embryogenic:** Embryonic lethality [76] |
| *Usp25*$^{-/-}$ | Systemic | NA | **Immune:** Higher incidence of septic shock induced by lipopolysaccharide [504]; More susceptible to H5N1 or HSV-1 infection [95]; Enhanced pathology of experimental autoimmune encephalomyelitis [111] |
| *Usp28*$^{-/-}$ | Systemic | **Liver cancer:** Higher susceptibility of liver carcinogenesis induced by diethylnitrosamine [255] | NA |
| *Usp28*$^{-/-}$ | Conditional (gut epithelium) | **Unspecified:** Ameliorated tumorigenesis and extended lifespan among Apc$^{min/+}$ mice [254] | **Digestive:** Reduced intestinal proliferation and impaired differentiation of secretory lineage cells [254]; |
| *Usp34*$^{-/-}$ | Conditional (mesenchymal stem cell) | NA | **Osteogenic:** Low bone mass [505] |
| *Usp36*$^{-/-}$ | Systemic | NA | **Embryogenic:** Embryonic lethality [77] |
| *Usp38*$^{-/-}$ | Systemic | NA | **Immune:** More potent antiviral responses against viral infection [92]; Alleviated allergic asthma induced by allergens [506] |
| *Usp44*$^{-/-}$ | Systemic | **Lung cancer:** Development of spontaneous tumors, especially lung cancer [507] | NA |
| *Usp46*$^{-/-}$ | Systemic | NA | **Nervous:** Significantly shorter immobility times than the wild-type mice in tail suspension test [508]; Significant behavioral alterations that might be related to mental disorders [509] |
| *Usp49*$^{-/-}$ | Systemic | **Colorectal cancer:** More susceptible to AOM/DSS-induced colorectal cancer [191] | NA |
| *Usp54*$^{-/-}$ | Systemic | **Colorectal cancer:** Resistant to chemically-induced colorectal cancer [98] | **Endocrinal:** Increased fat accumulation in female mice [98] |
| *Cyld*$^{-/-}$ | Systemic | **Colorectal cancer:** More susceptible to induced colonic inflammation and subsequent tumorigenesis [164]<br>**Liver cancer:** Highly sensitive to liver tumor development induced by diethylnitrosamine [162]<br>**Lung cancer:** Greater metastasis of transplanted lung cancer cells [165]<br>**Skin cancer:** Highly sensitive to skin tumor development induced by dimethylbenzanthracene and tetradecanoylphorbol acetate [163] | **Immune:** Lymphoid organ abnormalities and B cell hyperplasia [510]; Defective T-cell and NKT cell development [89,511]; Hypersusceptible to E.coli pneumonia [512]; Significantly less lethal listeriosis and liver pathology [513]; Protecting mice against acute lung injury, development of lung fibrosis and lethality after infection with Streptococcus pneumonia [294,514]; Early death after viral infection due to deteriorated host defense [515]; Spontaneous development of autoimmune symptoms and colonic inflammation [516]<br>**Nervous:** Alleviated symptoms of posttraumatic brain damage [517]<br>**Cardiovascular:** Ameliorated myocardial oxidative stress, cardiac maladaptive remodeling and heart failure after pathological pressure overload [85]<br>**Digestive:** Highly susceptible to hepatocellular damage, inflammation, and fibrosis [518]<br>**Reproductive:** Male infertility with significantly smaller testis size [105]<br>**Osteogenic:** Osteoporosis with abnormal osteoclasts [519]; Polydactyly and ciliary defects in multiple organs [520] |
| | Conditional (liver) | **Liver cancer:** Spontaneous development of hepatocyte apoptosis, liver fibrosis, biliary damage and hepatocellular carcinoma [166,167] | **Nervous:** Altered striatal rhythmic activity [521]<br>**Digestive:** Significantly higher liver versus body weight ratio [99,166] |

autoimmunity [71]. On the contrary, knockout of *Usp18* or *Usp25* suppresses immune responses, resulting in lower incidences of autoimmune diabetes [93], experimental autoimmune encephalomyelitis [94], and higher susceptibility to virus infection [95].

Similarly, USPs also demonstrate extensive participation in regulating endocrine homeostasis. Deletion of *Usp4* [96], *Usp10* [97], *Usp18* [22], *Usp54* [98] or *Cyld* [99] leads to increased insulin resistance, liver steatosis, and body fat accumulation among mouse models, while transgenic overexpression of *Usp2* [100], *Usp4* [96], *Usp10* [97] or *Usp18* [22] displays protective function against high-fat diet-induced metabolic disorders. However, despite of the protective effects from other USPs, systemic knockout of *Usp19* seems to enhance

metabolic resistance towards glucocorticoids [101,102] and high-fat diet [103], which suggests that USP19 might normally serve as a key regulator in metabolic homeostasis.

Additionally, genetic deletion of *Usp1*, *Usp2*, *Usp9X* or *Cyld* results in male infertility with defective fertilization, sperm motility, and smaller testis size [69,86,104–106]. Moreover, the nervous system is also widely influenced by diverse USPs [107–111], which further verifies the physiological significances of USPs for the development and function of mammalian organ system.

*2.1.3. Neoplastic roles of USPs-evidence from knockout and transgenic mouse models, clinical specimens and biochemical interactions*

*2.1.3.1. Oncogenic USPs*. Nearly half of the identified USPs display potential oncogenic functions, among which USP2, USP7, USP14 and USP17 are most extensively investigated (Table 3).

*2.1.3.1.1. USP2*. USP2 is a critical member of the USP family with extensive involvement in cancer progression. Although cancer-relevant knockout or transgenic mouse models are lacking, aberrantly elevated USP2 expression has been discovered in multiple types of human malignancies compared to normal adjacent tissues, such as glioma [112], breast cancer [113], ovarian cancer [114] and prostate cancer [115] (Table 3). Meanwhile, USP2 also acts as an unfavorable prognostic indicator among patients with glioma and breast cancer [112,113], which further suggests its potential oncogenic functions. With regard to its downstream mechanisms, elevated USP2 can deubiquitylate and stabilize multiple downstream substrates (Tables 2 and 3), such as Mdm2 [116], MdmX [117], cyclin D1 [118], FAS [115], TGFBR1 [119] and cyclin A1 [120]. These substrates either act as cell cycle regulators that promote cell survival and proliferation and inhibit apoptosis [118]. Mechanistically, USP2 substrates could either serve as transcriptional factors that are responsible for inducing expression of onco-proteins or E3 ubiquitin ligases that degrade tumor suppressors such as p53 [116], thereby contributing to the oncogenic transformation of normal cells. In terms of its upstream regulation in cancer, USP2 can be phosphorylated by TGFBR2, which is critical for its enzymatic activity as a DUB. This indicates that USP2 activity can be enhanced by oncogenic pathways such as TGF-β signaling pathway to induce cancer metastasis [119]. However, the identities of other upstream regulatory mechanisms especially those responsible for its overexpression in tumor cells remain undefined (Fig. 4).

*2.1.3.1.2. USP7*. USP7, also referred to as HAUSP, is another USP member with oncogenic potential. Overexpression of USP7 has been verified in various cancer tissues, including lung cancer [121] and hematological cancers such as multiple myeloma [122] and leukemia [123] (Table 3). Elevated expression of USP7 is correlated with lower differentiation status of neoplastic cells in breast cancer [124], ovarian cancer [125] and lung cancer [121]. Moreover, its expression level is associated with poor outcomes among colorectal [126], glioma [127], multiple myeloma [122], liver [128] and cervical [129] cancers, indicating a broad participation of USP7 in malignant transformation and progression. Regarding its downstream mechanism, USP7 deubiquitylates multiple substrates to engage in oncogenic activities (Tables 2 and 3). Both Mdm2 [130,131] and MdmX [132] could be stabilized by USP7, which counteracts the tumor-suppressive effects of p53 in tumorigenesis. In addition, both β-Catenin [133] and DNMT1 [134] are directly targeted and deubiquitylated by USP7 in colorectal cancer, which induce activation of the Wnt pathway and anti-apoptotic response respectively, leading to increased growth and drug resistance. Besides regulating its substrate stabilization on most circumstances, USP7 also induces nuclear export of PTEN, which inhibits PTEN activity to promote prostate cancer progression [135]. With regard to the upstream regulatory mechanisms of USP7, BCR-ABL could physically interact with and phosphorylate USP7 on its tyrosine residues, thus stimulates its enzymatic activity towards PTEN in leukemia cells [136]. Meanwhile, WDR79 serves as a scaffold protein to actively recruit USP7 and enhance its activity, which is critical for deubiquitylation of its downstream substrate Mdm2 and promotion of lung cancer cell proliferation [137]. BRE also recruits and directly interacts with USP7, which consequently activates its enzymatic activity towards CDC25A in cancer cells [138]. However, the details of the recruiting mechanisms as well as the molecular basis of USP7 overexpression in malignant cells remain largely unclear. Overall, although experimental evidence has suggested a oncogenic nature of USP7, we could only characterize USP7 as a potential oncogenic USP because no knockout or transgenic mouse models have been reported to confirm this notion (Fig. 4).

*2.1.3.1.3. USP14*. The clinical implications of USP14 among human malignancies have been extensively investigated. USP14 is overexpressed in solid tumors such as gastric [139] and lung [140] cancer, as well as hematological neoplasms including multiple myeloma [141] and lymphoma [142] (Table 3). Consistently, higher expression of USP14 indicates poor prognosis among patients with gastric [139], melanoma [143], esophageal [144], breast [145], liver [146], ovarian [147] and lung [140] cancers. Mechanistically, several cancer-related USP14 substrates have been identified, including Dvl [148], Vimentin [144], Aurora B [149] and AR (androgen receptor) [150] (Tables 2 and 3). The stabilization of these substrates either contributes to activation of oncogenic pathways such as the Wnt signaling, or promotes mitotic progression and epithelial-mesenchymal transition (EMT), which ultimately contributes to malignant behaviors of gastric, leukemia and prostate cancers [144,148–150]. The enzymatic activity and expression level of USP14 is regulated by upstream signaling pathways in cancers. Specifically, AKT is reported to phosphorylate USP14 at Ser432 and activates its deubiquitylating activity, which promotes tumorigenesis [151]. In additions, elevated expression of USP14 in cancer cells is at least partially attributed to decreased levels of its inhibitory miRNAs. For example, miR-320a is often found down-regulated in gastric cancer, which unleashes its suppressive effect on USP14 expression to promote gastric carcinogenesis [144]. Meanwhile, loss of miR-124a results in stronger stemness and gefitinib resistance of non-small cell lung cancer cells in part by elevating USP14 expression [152]. Overall, based on available evidence, we believe that it is appropriate to designate USP14 as a potential oncogenic USP in a variety of cancers due to lack of convincing data using genetically modified mouse models (Fig. 4).

*2.1.3.1.4. USP17*. USP17 is another important USP with a potential oncogenic role in multiple cancers. Despite a lack of evidence from hematological malignancies, overexpression of USP17 has been observed in a wide spectrum of solid cancers, such as breast [153] and colon [154] cancer (Table 3). Furthermore, overexpression of USP17 serves as an unfavorable indictor of overall and recurrence-free survival in several types of cancers, including lung [155,156] and ovarian [157] cancer. Recently, biochemical data has disclosed major substrates of USP17 in cancer cells, the stabilization of which may induce cancer progression especially in terms of cancer metastasis (Tables 2 and 3). Taking breast cancer as an example, USP17 interacts, deubiquitylates and stabilizes its substrates including Slug [158], Snail [159] and Twist [158] in cancer cells, which act as core regulators of EMT and consequently promote malignant migration and invasion. Moreover, SMAD4 is also targeted and stabilized by USP17 in osteosarcoma cells, leading to EMT and cancer invasiveness [160]. Besides a role in cancer metastasis, USP17 could also induce drug resistance in prostate cancer by stabilizing BRD4, implying a possible therapeutic strategy by targeting USP17 in BET inhibitor-resistant prostate cancer cells [161]. In contrast to extensive understanding on downstream mechanisms, however, little is known on the upstream regulatory events on USP17 in cancer.

Taken together, although the above-mentioned USPs have been widely investigated in different types of cancer, they could only be defined as potential oncogenic USPs due to lack of experimental evidence using genetically modified mouse models. Meanwhile, several other USPs also displayed oncogenic potential and are noteworthy

**Table 2**
Major cancer-relevant substrates of USPs.

| USPs | Substrates | Modifications | Major neoplastic consequences |
|---|---|---|---|
| USP1 | ULK1 | Stabilization | Guaranteeing the autophagy-dependent growth of breast cancer cells [522] |
| | EZH2 | Stabilization | Enhanced glioma cell proliferation [523] |
| | ID1/2/3 | Stabilization | Preservation of the mesenchymal stem cell program in osteosarcoma [69] |
| USP2 | cyclin D1 | Stabilization | Increased growth of multiple types of cancer cells [118] |
| | cyclin A1 | Stabilization | Enhancing bladder cancer progression [120] |
| | TGFBR1 | Altered activity | Enhancing lung cancer metastasis [119] |
| | FAS | Stabilization | Increased survival of prostate cancer cells [115] |
| | Mdm2 | Stabilization | Decreased cell death in prostate cancer [116] |
| | MdmX | Stabilization | Higher resistance to cisplatin treatment among testicular cancer cells [117] |
| USP3 | p53 | Stabilization | Suppressing cell proliferation and oncogenic transformation of somatic cells [194] |
| USP4 | HDAC2 | Stabilization | Promoting growth of breast cancer cells [451] |
| | TβRI | Stabilization | Promoting epithelial mesenchymal transition, invasion and metastasis of breast cancer cells [33] |
| | ARF-BP1 | Stabilization | Decreased sensitivity to chemotherapeutic agents of colon cancer cells [491] |
| | β-catenin | Stabilization | Enhanced transcriptional activity and malignant traits of colon cancer cells [524] |
| | PRL-3 | Stabilization | Potentiating colorectal oncogenesis [525] |
| | CypA | stabilization | Promoting liver cancer progression [526] |
| | TGFBR-1 | Stabilization | Promoting metastasis of liver cancer [527] |
| USP5 | c-Maf | Stabilization | Anti-apoptosis effects on multiple myeloma cells [473] |
| | FoxM1 | Stabilization | Promoting tumorigenesis and progression of pancreatic cancer [528] |
| USP6 | c-Jun | Stabilization | Promoting cancer cell invasion [529] |
| | Fzd | Stabilization | Promoting Wnt signaling and tumor growth [530] |
| | Jak1 | Stabilization | Increased cell survival and tumorigenesis [531] |
| USP7 (HAUSP) | CDC25A | Stabilization | Supporting tumor growth [138] |
| | HIF-1α | Stabilization | Inducing epithelial mesenchymal transition and promoting cancer metastasis [532] |
| | Mdm2 | Stabilization | Antagonizing p53-involved tumor suppression regulations [130,131] |
| | MdmX | Stabilization | Antagonizing p53-involved suppression regulations [132] |
| | PHF8 | Stabilization | Promoting breast carcinogenesis [124] |
| | Geminin | Stabilization | Promoting breast cancer progression [533] |
| | MDC1 | Stabilization | Promoting cervical cancer cell survival and conferring cellular resistance to genotoxic insults [129] |
| | β-catenin | Altered activity | Increased growth of colorectal cancer cells [133] |
| | DNMT1 | Stabilization | Decreased drug sensitivity in colon cancer [134] |
| | LSD1 | Stabilization | Promoting glioblastoma cell tumorigenesis and metastasis [127] |
| | NOTCH1 | Stabilization | Promoting cell growth of leukemia [534] |
| | TRIP12 | Stabilization | Triggering cell proliferation and invasion of liver cancer [128] |
| | CCDC6 | Stabilization | Enhanced tumor progression and drug resistance in lung cancer [535] |
| | Ki-67 | Stabilization | Promoting cell proliferation in lung cancer [121] |
| | NEK2 | Stabilization | Greater cell growth and drug resistance in multiple myeloma [536] |
| | N-Myc | Stabilization | Increased growth of neuroblastoma [537] |
| | AR | Stabilization | Promoting prostate cancer progression [538] |
| | PTEN | Subcellular localization | Promoting prostate cancer progression [135] |
| USP8 | Cx43 | Stabilization | Potential role in promoting progression of breast cancer [539] |
| | AIP4 | Altered activity | Possible role in inhibiting proliferation of glioblastoma [540] |
| USP9X | CLASPIN | Stabilization | Maintaining genomic stability and thus inhibiting tumorigenesis [541] |
| | pVHL | Stabilization | Inducing cancer cell proliferation [542] |
| | CEP131 | Stabilization | Promoting breast carcinogenesis [202] |
| | SMAD4 | Altered activity | Promoting breast cancer metastasis [543] |
| | SMURF1 | Stabilization | Maintaining cell motility of breast cancer cells [203] |
| | TDRD3 | Stabilization | Anti-apoptotic activity in breast cancer [210] |
| | TRB3 | Stabilization | Inducing breast cancer cell survival under hostile environment [211] |
| | YAP1 | Stabilization | Promoting breast cancer cell survival and chemo-resistance [204] |
| | β-catenin | Stabilization | Promoting growth of glioma cell [199] |
| | TTK | Stabilization | Promoting tumorigenesis of lung cancer [196] |
| | MCL1 | Stabilization | Promoting cell survival of lymphoma [197] |
| | XIAP | Stabilization | Increased growth and chemo-resistance in lymphoma [200] |
| | Ets-1 | Stabilization | Enhancing tumorigenicity in metastatic melanoma [544] |
| | IRS-2 | Stabilization | Promoting prostate cancer growth [545] |
| | FBW7 | Stabilization | Suppressing proliferation of colorectal cancer [195] |
| | AMOT | Stabilization | Suppressing malignant properties of kidney cancer [205] |
| | Itch | Stabilization | Suppressing pancreatic cancer progression [198] |
| | LATS2 | Stabilization | Inhibition on pancreatic cancer cell proliferation [206] |
| USP10 | Slug | Stabilization | Maintaining migratory ability of cancer cells [219] |
| | TOP2α | Altered activity | Possible role in promoting drug resistance in breast cancer [218] |
| | FLT3 | Stabilization | Maintaining the malignant traits of leukemia [220] |
| | G3BP2 | Stabilization | Promoting prostate oncogenesis [217] |
| | p53 | Stabilization | Suppressing cell growth of colon cancer [221] |
| | SIRT6 | Stabilization | Inhibition on colon oncogenesis [223] |
| | MSH2 | Stabilization | Increased apoptosis in lung cancer cells [222] |
| | p14ARF | Stabilization | Inhibition on lung cancer cell proliferation [546] |
| | AMPKα | Stabilization | Suppressing tumor progression in liver cancer [213] |
| | PTEN | Stabilization | Suppressing tumor progression in liver cancer [213] |

(*continued on next page*)

**Table 2** (*continued*)

| USPs | Substrates | Modifications | Major neoplastic consequences |
|---|---|---|---|
| USP11 | XIAP | Stabilization | Promotion of breast tumorigenesis [547] |
| | cIAP2 | Stabilization | Anti-apoptosis and increased drug resistance among colon cancer cells [548] |
| | eIF4B | Stabilization | Promoting oncogenesis of lymphoma [549] |
| | RAE1 | Stabilization | Increased cell proliferation of osteosarcoma cells [550] |
| | Mgl-1 | Stabilization | Inhibition on tumor formation [551] |
| | p21 | Stabilization | Tumor suppressive impacts [552] |
| | PML | Stabilization | Inhibiting tumorigenesis of glioma [553] |
| | VGLL4 | Stabilization | Inhibiting growth, migration and invasion of kidney cancer cells [554] |
| | XPC | Subcellular localization | Inhibition of skin carcinogenesis [555] |
| USP12 | AR | Stabilization | Increased survival of prostate cancer cells [556] |
| | Mdm2 | Stabilization | Maintaining malignant traits in prostate cancer cells [557] |
| USP13 | MCL1 | Stabilization | Enhancing tumor growth [558] |
| | c-Myc | Stabilization | Maintaining self-renewal and tumorigenic potential of glioblastoma stem cells [559] |
| | ACLY | Stabilization | Driving ovarian cancer metabolism [560] |
| | OGDH | Stabilization | Driving ovarian cancer metabolism [560] |
| | RAP80 | Stabilization | Promoting drug resistance among ovarian cancer cells [561] |
| | MITF | Stabilization | Increased melanoma cell proliferation [562] |
| | PTEN | Stabilization | Inhibition on breast tumorigenesis [563] |
| USP14 | Dvl | Stabilization | Activating oncogenic Wnt pathway [148] |
| | Vimentin | Stabilization | Contributing to the migration and invasion of gastric cancer [144] |
| | Aurora B | Stabilization | Inhibiting chemotherapeutic drugs-induced apoptosis in leukemia cells [149] |
| | AR | Stabilization | Promoting prostate cancer proliferation [150] |
| USP15 | Mdm2 | Stabilization | Promoting cancer cell survival and inhibiting anti-tumor T-cell responses [90] |
| | TβR-I | Stabilization | Higher activity of TGF-β pathway and glioblastoma oncogenesis [564] |
| | HBx | Stabilization | Possible role in promoting hepatic tumorigenesis [565] |
| | TOP2α | Altered activity | Possible role in promoting lung tumorigenesis [566] |
| | Keap1 | Altered activity | A reduction in Nrf2 target gene expression and decreased chemo-resistance [567] |
| | p53 | Stabilization | Tumor suppressive responses [568] |
| | IRS-2 | Altered activity | Suppression of proliferation signaling in prostate cancer [569] |
| USP17 | Cdc25A | Stabilization | Promoting oncogenesis of breast cancer [570] |
| | Geminin | Stabilization | Promoting breast cancer progression [533] |
| | Slug | Stabilization | Promoting metastasis of breast cancer cells [158] |
| | Snail | Stabilization | Promoting breast cancer metastasis [159] |
| | Twist | Stabilization | Promoting metastasis of breast cancer cells [158] |
| | HAS2 | Stabilization | Possible role in promoting lung tumorigenesis [571] |
| | SMAD4 | Stabilization | Promoting proliferation and metastasis of osteosarcoma [160] |
| | BRD4 | Stabilization | Promoting BET inhibitor resistance and prostate cancer progression [161] |
| USP18 | PML/RARα | Stabilization | Anti-apoptotic effects among leukemia cells [232] |
| | BCL2L1 | Stabilization | Maintaining the growth of liver cancer cells [231] |
| | KRAS | Stabilization | Promoting oncogenic consequences in lung cancer [228] |
| USP19 | HDAC1/2 | Altered activity | Possible role in maintaining genomic stability and suppressing oncogenic transformation [572] |
| USP20 | β-catenin | Stabilization | Inducing proliferation, invasion and migration of cancer cells [573] |
| | CLASPIN | Stabilization | Promoting genomic stability and suppressing tumor growth [574] |
| | Tax | Altered activity | Suppressing oncogenesis of T-cell leukemia [575] |
| | TRAF6 | Altered activity | Suppressing oncogenesis of T-cell leukemia [575] |
| USP21 | EZH2 | Stabilization | Promoting cell proliferation and metastasis in bladder cancer [576] |
| | BRCA2 | Stabilization | Repair of DNA damage and promoting liver cancer growth [577] |
| | MEK2 | Stabilization | Promoting liver cancer growth [578] |
| | MARK1 | Stabilization | Anti-tumor effects [579] |
| USP22 | CCNB1 | Stabilization | Cancer cell growth [95] |
| | CCND1 | Stabilization | Possible role in promoting oncogenic transformation [580] |
| | FBP1 | Altered activity | Enhanced cancer cell growth [581] |
| | c-Myc | Stabilization | Increased growth and migration of breast cancer cells [582] |
| | KDM1A | Stabilization | Cancer stem cell self-renewal and glioblastoma tumorigenesis [542] |
| | BMI1 | Stabilization | Maintaining glioma malignancy [539] |
| | SIRT1 | Stabilization | Promoting multi-drug resistance of liver cancer [583] |
| | COX-2 | Stabilization | Promoting proliferation of lung cancer cells [241] |
| | EGFR | Stabilization | Promoting cell proliferation, migration and invasion, and resistance to EGFR-TKIs in EGFR mutant lung cancer cells [240] |
| | H2A | Altered activity | Inducing cisplatin resistance in lung cancer [242] |
| | PU.1 | Stabilization | Rescuing leukemogenesis and inducing normal hematopoietic differentiation [253] |
| USP24 | β-TrCP | Stabilization | Promoting lung cancer malignancy [584] |
| | MCL-1 | Stabilization | Maintaining cell survival of multiple myeloma [481] |
| | Bax | Stabilization | Increased cell apoptosis in early lung cancer formation [585] |
| | E2F4 | Stabilization | Increased cell apoptosis in early lung cancer formation [585] |
| | p300 | Stabilization | Increased cell apoptosis in early lung cancer formation [585] |
| | Securin | Stabilization | Increased cell apoptosis in early lung cancer formation [585] |
| USP26 | AR | Altered activity | Possible role in triggering oncogenesis of prostate cancer [586] |
| | SMAD7 | Stabilization | Possible role in suppressing glioblastoma pathogenesis [587] |
| USP27 | Cyclin E | Stabilization | Inducing hepatocellular tumorigenesis [588] |

(*continued on next page*)

**Table 2** (*continued*)

| USPs | Substrates | Modifications | Major neoplastic consequences |
|---|---|---|---|
| USP28 | c-Myc | Stabilization | Tumor cell proliferation [260] |
| | Fbw7 | Stabilization | Maintaining oncogenic traits [261] |
| | LIN28A | Stabilization | Enhancing cancer cell viability and migration [262] |
| | LSD1 | Stabilization | Tumorigenic activities among breast cancer cells [263] |
| | c-Jun | Stabilization | Promoting colorectal oncogenesis [254] |
| | NICD1 | Stabilization | Promoting colorectal oncogenesis [254] |
| | p53 | Stabilization | Possible role in inducing cell cycle arrest among cancer cells [264] |
| USP29 | Claspin | Stabilization | Possible role in promoting cell cycle progression in cancer cells [589] |
| | p53 | Stabilization | Increased apoptosis of cancer cells in response to oxidative stress [590] |
| USP30 | TOM20 | Stabilization | Anti-apoptotic effects among cancer cells [591] |
| | DRP1 | Stabilization | Promoting hepatocarcinogenesis [592] |
| USP33 | PPM1A | Stabilization | Suppression on cancer metastasis [593] |
| | Robo1 | Stabilization | Inhibitory function on breast cancer cell migration [594] |
| | β-arrestin2 | Altered activity | Inhibitory impacts on ERK activation among colorectal cancer cells [595] |
| USP35 | ABIN-2 | Stabilization | Tumor inhibition [596] |
| USP36 | c-Myc | Stabilization | Promoting cancer cell proliferation [597] |
| | DHX33 | Stabilization | Maintaining cancer cell survival [77] |
| | H2B | Altered activity | Increased cancer cell proliferation [598] |
| | CHD7 | Stabilization | Promoting development of neuroblastoma [599] |
| USP37 | 14–3-3γ | Stabilization | Malignant transformation and increased migration among cancer cells [600] |
| | PLZF/RARA | Stabilization | Oncogenic transformation of acute promyelocytic leukemia [601] |
| | c-Myc | Stabilization | Promoting cell proliferation of lung cancer [602] |
| | p27 | Stabilization | Blocked proliferation of medulloblastoma cells [603] |
| USP38 | LSD1 | Stabilization | Promoting malignant traits in colon cancer cells [604] |
| USP42 | p53 | Stabilization | Possible role in oncogenic cell cycle arrest [605] |
| USP43 | H2B | Altered activity | Inhibitory effects on breast carcinogenesis [604] |
| USP44 | H2B | Altered activity | Maintaining efficient invasiveness of triple-negative breast cancer cells [606] |
| | Securin | Stabilization | Enhanced malignancy of glioma [607] |
| USP46 | Cdt2 | Stabilization | Promoting cell proliferation in cervical cancer [608] |
| | PHLPP | Stabilization | Tumor-suppressive impacts in colorectal cancer [609] |
| USP47 | β-catenin | Stabilization | Cancer cell growth [610] |
| | Snail | Stabilization | Triggering the epithelial-mesenchymal transition and metastasis of colon cancer cells [611] |
| USP48 | TRAF2 | Stabilization | Potential role in promoting cancer metastasis [191] |
| | Gli1 | Stabilization | Promoting glioblastoma tumorigenesis [612] |
| USP49 | p53 | Stabilization | Tumor inhibition [191] |
| | FKBP51 | Stabilization | Inhibited cell proliferation and enhanced drug sensitivity of pancreatic cancer [193] |
| USP51 | ZEB1 | Stabilization | Promoting oncogenesis in breast cancer [613] |
| USP52 | ASF1A | Stabilization | Cell growth and drug resistance in breast cancer [614] |
| CYLD | Dvl | Altered activity | Suppressing Wnt signaling and tumorigenesis [174] |
| | p53 | Stabilization | Anti-tumor responses in multiple malignancies [175] |
| | TRAF2 | Altered activity | Tumor suppressive effects by enhancing cell apoptosis [176] |
| | Bcl-3 | Altered activity | Inhibition on skin carcinogenesis [163] |

Note: Substrates should directly interact with and then be deubiquitylated by its corresponding DUBs based on the catalytic enzymatic functions. Those feature non-catalytical interactions with or deubiquitylation by DUBs should not be considered as substrates.

(Table 3), such as USP54. Systemic knockout of *Usp54* induces resistance to chemically induced colorectal cancer [98], which is a solid evidence demonstrating its oncogenic role. Nonetheless, little is known about its upstream regulatory mechanisms as well as pathological implication in clinical settings.

*2.1.3.2. Tumor-suppressive USPs.* Unlike the huge amount of oncogenic USPs, only less than ten USPs have been verified with tumor-suppressive potential, among which CYLD stands out as the most typical one (Table 4).

*2.1.3.2.1. CYLD.* Currently, several knockout mouse models have consistently proven the tumor-inhibitory effects of CYLD on diverse cancers. Specifically, systemic knockout of *Cyld* increases the susceptibility of liver carcinogenesis induced by diethylnitrosamine [162], skin cancer development induced by dimethylbenzanthracene (DMBA) and tetradecanoylphorbol acetate (TPA) [163], as well as colon tumorigensis triggered by colonic inflammation [164]. Meanwhile, increased metastasis of transplanted lung cancer cells has also been observed among *Cyld*-deficient mouse models [165]. Moreover, conditional ablation of *Cyld* among hepatic cells also culminates in spontaneous development of hepatocellular carcinoma [166,167]. With regard to pathological evidence, CYLD is downregulated in different cancers, such as pancreatic cancer [168], lung cancer [169], leukemia [170] and multiple myeloma [171]. Higher expression of CYLD also indicates better survival prognosis among patients with breast cancer [172], oral squamous cell carcinoma [173], multiple myeloma [171] and neuroblastoma [45]. Several downstream substrates have been identified to mediate the tumor-suppressive role of CYLD, including Dvl [174], p53 [175], TRAF2 [176] and Bcl-3 [163] (Tables 2 and 4). For example, deubiquitylation of Dvl by CYLD leads to significant inhibition of the oncogenic Wnt pathway and suppresses tumorigenesis [174]. In addition, CYLD also deubiquitylates and stabilizes p53, a critical tumor suppressor in human malignancies, to execute broad-range anti-tumor effects [175]. Moreover, CYLD is reported to bind and deubiquitylate both TRAF2 and Bcl-3 to suppress NF-κB signaling, thereby inhibiting oncogenic transformation in keratinocytes [163,176].

Unlike other tumor-suppressive USPs, the upstream mechanisms regulating the expression and activity of CYLD in cancer have also been extensively studied. In this regard, CYLD expression is regulated at the transcriptional, post-transcriptional, and post-translational levels among different types of cancer cells. Oncogenic signaling pathways downregulate expression of CYLD through several transcription factors, including Snail in melanoma [177], Hes1 of the Notch signaling pathway in T-cell leukemia [178], Gli1 of the Hedgehog signaling pathway in basal cell carcinoma [179] and LEF1 of the Wnt/β-catenin pathway in chronic lymphocytic leukemia [170]. Nearly a dozen of miRNAs, at the post-transcriptional levels, was reported to inhibit CYLD

**Table 3**
Major oncogenic USPs.

| USPs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Major pathological evidence (cancer relevant human specimens) | Major biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| USP1 | NA | **Overexpressed** in breast cancer [522], multiple myeloma [457], glioblastoma [615], lung cancer [616], osteosarcoma [69] | **Breast cancer:** ULK1 [522]; **Glioma:** EZH2 [523]; **Osteosarcoma:** ID1/2/3 [69] | Potential |
| USP2 | NA | **Overexpressed** in glioma [112], breast cancer [113], ovarian cancer [114], prostate cancer [115] | **Unspecified**: cyclin D1 [118]; **Bladder cancer:** cyclin A1 [120]; **Lung cancer:** TGFBR1 [119]; **Prostate cancer:** FAS [115], Mdm2 [116]; **Testicular cancer:** MdmX [117] | Potential |
| USP4 | NA | **Overexpressed** in esophageal cancer [617], colorectal cancer [525], liver cancer [526], melanoma [618], head and neck squamous cell cancer [619] | **Breast cancer:** HDAC2 [451], TβRI [33]; **Colorectal cancer:** ARF-BP1 [491], β-catenin [524], PRL-3 [525]; **Liver cancer:** CypA [526], TGFR-1 [527] | Potential |
| USP5 | NA | **Overexpressed** in pancreatic cancer [620], multiple myeloma [473], liver cancer [621] | **Multiple myeloma:** c-Maf [473]; **Pancreatic cancer:** FoxM1 [528] | Potential |
| USP6 | NA | **Overexpressed** in colon cancer [622], Ewing sarcoma [623] | **Unspecified**: c-Jun [529], Fzd [530], Jak1 [531] | Potential |
| USP7 | NA | **Overexpressed** in esophageal cancer [155], cervical cancer [129], liver cancer [128], breast cancer [124], leukemia [123], prostate cancer [624], colorectal cancer [126], ovarian cancer [125], glioma [127], lung cancer [121], multiple myeloma [122] | **Unspecified**: CDC25A [138], HIF-1α [532], Mdm2 [130,131], MdmX [132]; **Breast cancer:** PHF8 [124], Geminin [533]; **Cervical cancer:** MDC1 [129]; **Colorectal cancer:** β-Catenin [133], DNMT1 [134]; **Glioblastoma:** LSD1 [127]; **Leukemia:** NOTCH1 [534]; **Liver cancer:** TRIP12 [128]; **Lung cancer:** CCDC6 [535], Ki-67 [121]; **Multiple myeloma:** NEK2 [536]; **Neuroblastoma:** N-Myc [537]; **Prostate cancer:** AR [538], PTEN [135] | Potential |
| USP12 | NA | **Overexpressed** in prostate cancer [557] | **Prostate cancer:** AR [556], Mdm2 [557] | Potential |
| USP14 | NA | **Overexpressed** in gastric cancer [139], esophageal cancer [144], lymphoma [142], oral squamous cell cancer [625], breast cancer [145], liver cancer [146], ovarian cancer [147], multiple myeloma [141], colorectal cancer [148,626], lung cancer [140], intrahepatic cholangiocarcinoma [627] | **Unspecified:** Dvl [148]; **Gastric cancer:** Vimentin [144]; **Leukemia:** Aurora B [149]; **Prostate cancer:** AR [150] | Potential |
| USP17 | NA | **Overexpressed** in lung cancer [571], colon cancer [154], esophageal cancer [154], cervical cancer [154], prostate cancer [161], breast cancer [153], ovarian cancer [157] | **Breast cancer:** Cdc25A [570], Geminin [533], Slug [158], Snail [159], Twist [158]; **Lung cancer:** HAS2 [571]; **Osteosarcoma:** SMAD4 [160]; **Prostate cancer:** BRD4 [161] | Potential |
| USP25 | NA | **Overexpressed** in lung cancer [224] | NA | Potential |
| USP27 | NA | **Overexpressed** in liver cancer [588] | **Liver cancer:** Cyclin E [588] | Potential |
| USP30 | NA | NA | **Unspecified:** TOM20 [591]; **Liver cancer:** DRP1 [592] | Less potential |
| USP32 | NA | **Overexpressed** in lung cancer [628] | NA | Potential |
| USP34 | NA | **Overexpressed** in lymphoma [629] | NA | Potential |
| USP36 | NA | **Overexpressed** in breast cancer [597], ovarian cancer [630] | **Unspecified:** c-Myc [597], DHX33 [77], H2B [598]; **Neuroblastoma:** CHD7 [599] | Potential |
| USP38 | NA | NA | **Colorectal cancer:** LSD1 [604] | Less potential |
| USP39 | NA | **Overexpressed** in pancreatic cancer [631], colorectal cancer [632], lung cancer [633], melanoma [199], prostate cancer [634], liver cancer [635], breast cancer [636] | NA | Potential |
| USP47 | NA | **Overexpressed** in colorectal cancer [611] | **Unspecified:** β-catenin [610]; **Colon cancer:** Snail [611] | Potential |
| USP48 | NA | **Overexpressed** in glioma [612] | **Unspecified:** TRAF2 [191]; **Glioblastoma:** Gli1 [612] | Potential |
| USP51 | NA | **Overexpressed** in breast cancer [613] | **Breast cancer:** ZEB1 [613] | Potential |
| USP52 | NA | **Overexpressed** in breast cancer [614] | **Breast cancer:** ASF1A [614] | Potential |
| USP54 | Systemic *Usp54*$^{-/-}$ induces resistance to chemically-induced colorectal cancer [98] | NA | NA | Strong |
| **USPs** | **Physiological evidence (cancer relevant knockout or transgenic mouse models)** | **Pathological evidence (cancer relevant human specimens)** | **Biochemical evidence (cancer relevant substrates)** | **Evidence grade** |
| USP3 | Systemic *Usp3*$^{-/-}$ increases incidences of tumorigenesis [87] | **Downregulated** in colorectal cancer [192] | **Unspecified**: p53 [194] | Strong |
| USP16 | NA | **Downregulated** in liver cancer [637] | NA | Potential |
| USP19 | NA | **Downregulated** in kidney cancer [572] | **Unspecified**: HDAC1/2 [572] | Potential |
| USP33 | NA | **Downregulated** in lung cancer [638], gastric cancer [639], thyroid cancer [640], colorectal cancer [595] | **Unspecified:** PPM1A [593]; **Breast cancer:** Robo1 [594]; **Colorectal cancer:** β-arrestin2 [595] | Potential |
| USP35 | NA | **Downregulated** in breast cancer [596] | **Unspecified:** ABIN-2 [596] | Potential |

(*continued on next page*)

**Table 3** (*continued*)

| USPs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Major pathological evidence (cancer relevant human specimens) | Major biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| USP43 | NA | **Downregulated** in breast cancer [604] | **Breast cancer:** H2B [604] | Potential |
| USP49 | Systemic *Usp49*$^{-/-}$ leads to higher susceptibility to AOM/DSS-induced colorectal cancer [191] | **Downregulated** in pancreatic cancer [193] | **Unspecified:** p53 [191]; **Pancreatic cancer:** FKBP51 [193] | Strong |
| CYLD | 1. Systemic *Cyld*$^{-/-}$ leads to greater metastasis of transplanted lung cancer cells [165]; 2. Systemic *Cyld*$^{-/-}$ results in higher sensitivity to liver tumor development induced by diethylnitrosamine [162]; 3. Systemic *Cyld*$^{-/-}$ induces higher susceptibility to skin tumor development induced by dimethylbenzanthracene and tetradecanoylphorbol acetate [163]; 4. Systemic *Cyld*$^{-/-}$ mice are more susceptible to induced colonic inflammation and subsequent tumorigenesis [164]; 5. Conditional *Cyld*$^{-/-}$ culminates in spontaneous development of hepatocellular carcinoma [166,167] | **Downregulated** in pancreatic cancer [168], cervical cancer [641], lung cancer [169], liver cancer [180], breast cancer [172], melanoma [642], oral squamous cell carcinoma [173], multiple myeloma [171], leukemia [170] | **Unspecified:** Dvl [174], p53 [175], TRAF2 [176]; **Skin cancer:** Bcl-3 [163] | Strong |

Note: Based on different credibility of biological evidence, if the oncogenic role of one USP is confirmed by genetically-modified mouse models, then the evidence grade is strong. Otherwise, the grades are designated as potential and less potential in terms of pathological and biochemical evidence respectively.

expression, which ultimately leads to malignant behavious in various types of cancer. These miRNAs include miRNA-362-5p in hepatocellular carcinoma [180], miR-19 in T-cell acute lymphoblastic leukemia [181] and miR-181b in esophageal cancer [182]. Additionally, at the post-translational levels, HPV encoded E6 proteins promotes ubiquitylation and proteasomal degradation of CYLD in hypoxic and infected cells, subsequently resulting in NF-κB activation to facilitate HPV-associated malignancies [183,184]. Other upstream regulatory mechanisms of CYLD enzymatic activity include post-translational modifications and allosteric activation. Phosphorylation of Serine 418 on CYLD by IKBKE decreases the deubiquitylating activity of CYLD to induce oncogenic transformation of mammary cells [185]. Meanwhile, the enzymatic activity of CYLD could also be inhibited by SUMOylation, which contributes to the proliferation of neuroblastoma cells [45]. On the other hand, SPATA2 acts as an allosteric activator of CYLD, which suppresses major oncogenic pathways including NF-κB and MAPK [186]. Apart from the upstream regulatory mechanisms, loss-of-function mutations of CYLD contribute to malignant development in certain types of cancer, such as nasopharyngeal cancer [187], multiple myeloma [188], adenoid cystic carcinoma [189] and skin squamous cell cancer [190]. Therefore, based on our current knowledge, CYLD may serve as a major tumor suppressor in multiple types of human malignancies. From a genetic perspective, some transgenic mouse models will provide more solid evidence to demonstrate a tumor-suppressive role of CYLD (Fig. 5).

Besides CYLD, there is also strong evidence about other USPs, such as USP3 and USP49, with tumor-suppressive roles in cancer development (Table 4). Systemic ablation of *Usp3* increases incidence of tumorigenesis [87] while global knockout of *Usp49* also leads to higher susceptibility to AOM/DSS-induced colorectal cancer [191]. Meanwhile, downregulation of USP3 and USP49 have been found in colorectal cancer [192] and pancreatic cancer [193], respectively. Nevertheless, there is currently little knowledge on how they exert anti-tumor activity, as p53 is the only reported substrates of these two USPs [191,194]. Therefore, further investigation is warranted to elucidate the downstream regulatory mechanisms of both USP3 and USP49 in human tumorigenesis.

*2.1.3.3. Context-dependent USPs*. Apart from the specific oncogenic functions of many USPs mentioned above, there are also significant amount of USPs displaying both tumorigenic and tumor-suppressive roles among different types of malignancies, especially USP9X, USP10, USP18, USP22 and USP28 (Table 5).

*2.1.3.3.1. USP9X*. As for USP9X, despite lacking oncogenic models, its tumor-suppressive role has been confirmed by genetically-edited mouse models where systemic loss of *Usp9X* increases tumor burden in colitis-associated colorectal cancer [195], suggesting a tumor-suppressive role. However, overexpression of USP9X has been discovered in multiple types of malignancies, ranging from solid cancers such as lung cancer [196] to hematological malignancies such as multiple myeloma [197], indicating a tumor-supporting function. On the other hand, downregulated USP9X has also been credibly detected in certain types of cancers compared to normal tissues, including colorectal cancer [195] and pancreatic cancer [198] (Table 5). Consistently, USP9X may indicate contradictory clinical outcomes. USP9X serves as an unfavorable prognostic indicator among patients with glioma [199], lymphoma [200], multiple myeloma [197] and esophageal cancer [201], while its expression status correlates with better prognosis of colorectal cancer [195] and pancreatic [198] cancer patients.

In terms of its downstream mechanisms, the deubiquitylation and stabilization of different substrates by USP9X explains how USP9X expression is associated with distinct neoplastic consequences (Tables 2 and 5). For example, USP9X could directly stabilize CEP131 [202], SMURF1 [203] and YAP1 [204] in breast cancer cells. CEP131, as a key protein for centrosome amplification, disturbs cell division and induces

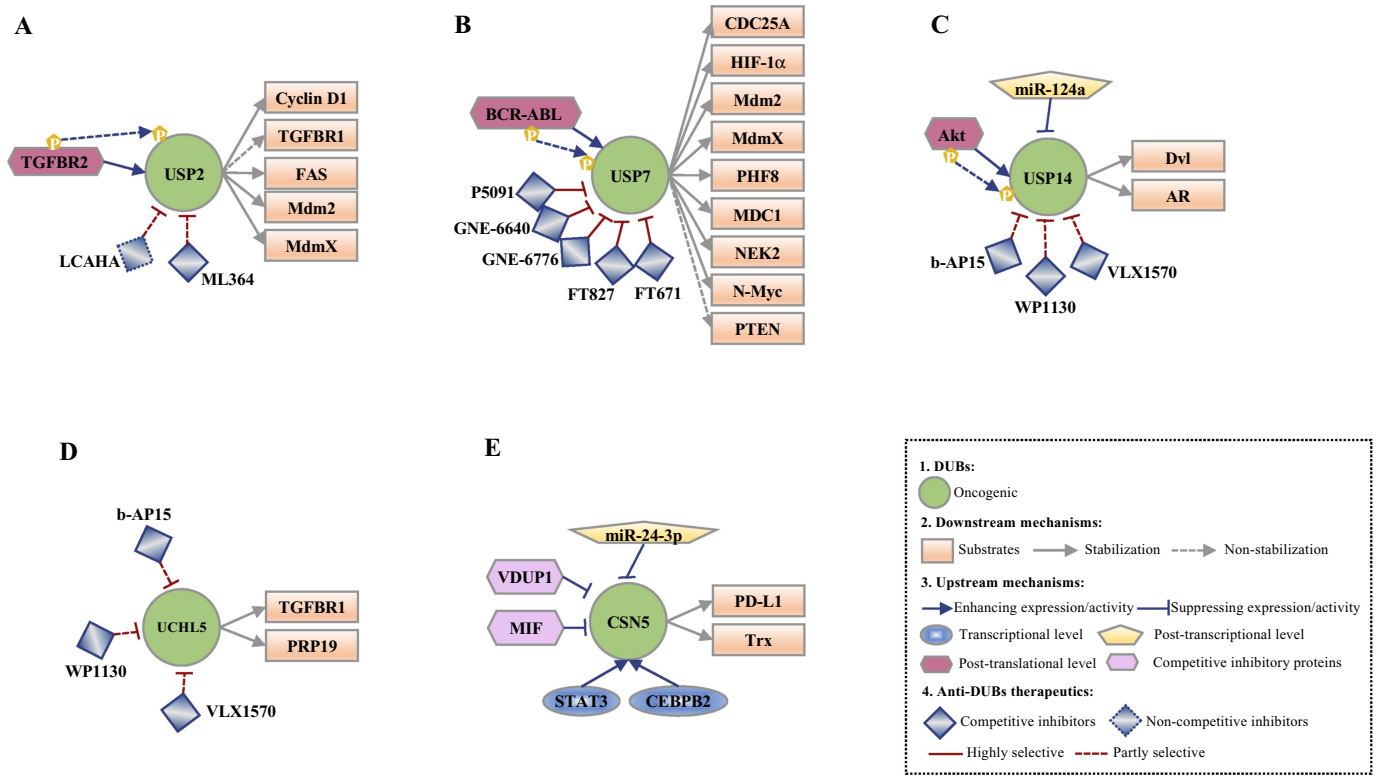


**Fig. 4.** Major downstream, upstream mechanisms as well as inhibitors of key oncogenic DUBs. A. USP2; B. USP7; C. USP14; D. UCHL5; E. CSN5.

tumorigenesis [202]. SMURF1 serves as a key E3 ligase to regulate cell migration [203] and YAP1 is a downstream transcriptional regulator of the Hippo pathway [204]. Therefore, by regulating these tumorigenic signaling pathways, USP9X may induce malignant transformation, cancer cell survival, distant metastasis as well as chemo-resistance of breast cancer. In terms of anti-tumor effects, USP9X stabilizes FBW7 (a tumor suppressor that targets oncoproteins such as c-MYC for ubiquitylation) [195], AMOT (a YAP1 inhibitor which limits the nuclear localization of YAP1 via direct physical association) [205] and LATS2 (a kinase that suppresses Hippo pathway) [206] to suppress colorectal cancer, kidney cancer and pancreatic cancer.

As a context-dependent USP, USP9X is regulated by several upstream molecular events in tumor cells. To this end, miR-212 [207], miR-132 [208] and miR-26b [209] could inhibit the metastasis of lung and liver cancer by downregulating USP9X, which suggests that targeting these microRNAs might upregulate USP9X in human cancers. Meanwhile, catalytic activity of USP9X is modulated by arginine methylation [210] as well as the USP9X-interacting partners TRB3 [211] and BAG3 [212]. Moreover, USP9X is downregulated in pancreatic cancer due to loss-of-function mutations [198]. Altogether, these findings suggest that USP9X might play a Janus-faced role in regulating the molecular networks that sustains tumorigenesis. Since there is lack of evidence from genetically modified mouse models, we think it is more appropriate to define USP9X as a potential context-dependent USP (Fig. 6).

*2.1.3.3.2. USP10.* USP10 is another potential context-dependent USP for human cancer. Downregulated USP10 has been identified in a variety of solid malignancies, such as liver [213] and lung [214] cancer. Moreover, higher expression of USP10 is often linked to better survival outcomes among patients with liver [213], small intestinal [215] and gastric [216] cancer. Nevertheless, overexpression of USP10 has also been detected in prostate cancer tissues as compared to adjacent controls, indicating an unfavorable prognosis among clinical patients as well [217] (Table 5). This evidence suggests that USP10 might have specific clinical implications depending on cancer types. In terms of its downstream mechanisms, the context-dependent role of USP10 depends on its deubiquitylating effects on various neoplastic substrates (Tables 2 and 5). For example, USP10 could deubiquitylate downstream substrates, such as G3BP2 [217], TOP2α [218], Slug [219] and FLT3 [220], to promote oncogenic transformation, migration, drug resistance of different human cancer. USP10 might also be tumor-suppressive by stabilizing the expression of diverse tumor suppressors, such as p53 in colon [221], MSH2 in lung [222] and PTEN in liver [213] cancers. Regardless of an oncogenic or tumor-suppressive role, USP10 substrates often engage in regulation of genomic integrity [218,222], or serve as transcription factors [219,221] and key mediators of neoplastic pathways [213,223], thereby leading to context-dependent neoplastic processes.

As for the upstream regulation, miRNA-191 directly inhibits the expression of USP10 to promote pancreatic cancer progression [224]. The enzymatic activity of USP10 may be attenuated by interacting with oncoprotein Tax via an unspecified mechanism, which might partially contribute to the oncogenesis of T-cell leukemia [225]. Meanwhile, Beclin1 is reported to maintain the deubiquitylating activity of USP10, leading to stabilized p53 to suppress tumorigenesis [226]. However, the upstream regulatory mechanisms of USP10 are still unclear, while its definite role in human tumorigenesis is yet to be determined using genetically modified mouse models (Fig. 6).

*2.1.3.3.3. USP18.* The context-dependent role of USP18 in neoplastic events has been clearly described based on knockout mouse models. Systemic depletion of *Usp18* reduces mammary tumor growth [227] and tumorigenicity of KRAS-driven lung cancer [228]. Likewise, conditional ablation of *Usp18* in bone marrow results in higher resistance to BCR-ABL–induced chronic myeloid leukemia in mouse models [229]. Conversely, global knockout of *Usp18* could induce spontaneous development of leiomyosarcoma [230], suggesting a tumor-suppressive role. In contrast to strong evidence offered by knockout mouse models, clinical pathological implications of

**Table 4**
Major tumor-suppressive USPs.

| USPs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Pathological evidence (cancer relevant human specimens) | Biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| USP3 | Systemic *Usp3*$^{-/-}$ increases incidences of tumorigenesis [87] | **Downregulated** in colorectal cancer [192] | **Unspecified:** p53 [194] | Strong |
| USP16 | NA | **Downregulated** in liver cancer [637] | NA | Potential |
| USP19 | NA | **Downregulated** in kidney cancer [572] | **Unspecified:** HDAC1/2 [572] | Potential |
| USP33 | NA | **Downregulated** in lung cancer [638], gastric cancer [639], thyroid cancer [640], colorectal cancer [595] | **Unspecified:** PPM1A [593]; **Breast cancer:** Robo1 [594]; **Colorectal cancer:** β-arrestin2 [595] | Potential |
| USP35 | NA | **Downregulated** in breast cancer [596] | **Unspecified:** ABIN-2 [596] | Potential |
| USP43 | NA | **Downregulated** in breast cancer [604] | **Breast cancer:** H2B [604] | Potential |
| USP49 | Systemic *Usp49*$^{-/-}$ leads to higher susceptibility to AOM/DSS-induced colorectal cancer [191] | **Downregulated** in pancreatic cancer [193] | **Unspecified:** p53 [191]; **Pancreatic cancer:** FKBP51 [193] | Strong |
| CYLD | 1. Systemic *Cyld*$^{-/-}$ leads to greater metastasis of transplanted lung cancer cells [165]; 2. Systemic *Cyld*$^{-/-}$ results in higher sensitivity to liver tumor development induced by diethylnitrosamine [162]; 3. Systemic *Cyld*$^{-/-}$ induces higher susceptibility to skin tumor development induced by dimethylbenzanthracene and tetradecanoylphorbol acetate [163]; 4. Systemic *Cyld*$^{-/-}$ mice are more susceptible to induced colonic inflammation and subsequent tumorigenesis [164]; 5. Conditional *Cyld*$^{-/-}$ culminates in spontaneous development of hepatocellular carcinoma [166,167] | **Downregulated** in pancreatic cancer [168], cervical cancer [641], lung cancer [169], liver cancer [180], breast cancer [172], melanoma [642], oral squamous cell carcinoma [173], multiple myeloma [171], leukemia [170] | **Unspecified:** Dvl [174], p53 [175], TRAF2 [176]; **Skin cancer:** Bcl-3 [163] | Strong |

Note: Based on different credibility of biological evidence, if the tumor-suppressive role of one USP is confirmed by genetically-modified mouse models, then the evidence grade is strong. Otherwise, the grades are designated as potential and less potential in terms of pathological and biochemical evidence respectively.

USP18 remain largely insufficient. Although overexpression of USP18 has been identified in liver [231] and lung [228] cancers (Table 5), there is limited pathological findings and prognostic analysis to support an anti-tumor function for USP18. Moreover, only oncogenic downstream substrates have been identified for USP18 (Tables 2 and 5). Specifically, by stabilizing PML/RARα, USP18 promotes the oncogenic transcription and then enhances the growth of acute promyelocytic leukemia [232]. USP18 also deubiquitylates and stabilizes BCL2L1 to inhibit cell apoptosis in hepatocellular carcinoma [231]. Meanwhile, USP18 can maintain the stability of KRAS, a critical oncoprotein, to support malignant phenotypes of lung cancer cells [228]. Furthermore, the upstream mechanisms regulating USP18 expression and activity are still largely unknown. Therefore, although the evidence is strong for a context-dependent role of USP18 in cancer, further studies are required to explore the pathological implications and mechanistic insights into the anti-tumor role of USP18 in various types of human cancers.

*2.1.3.3.4. USP22.* USP22 is another broadly investigated context-dependent USP member. Despite a lack of oncogenic evidence based on genetically-modified mouse models, the tumorigenic role of USP22 has been implied in both clinical samples and biochemical analyses (Table 5). USP22 is overexpressed in a variety of human solid tumors, while its upregulation in cancerous tissues is linked to poor prognosis among cancer patients, especially for those with lung [233,234], colorectal [235,236] or liver [237–239] cancers. Similar to other USPs, the oncogenic consequence of elevated USP22 also mainly rely on its deubiquitylation on downstream substrates (Tables 2 and 5). For instance, USP22 could either stabilize or alter the activity of its substrates, including EGFR [240], COX-2 [241] and H2A [242], which impact oncogenic pathways, inflammatory signaling and transcriptional activity respectively and subsequently enhance nearly every aspects of lung tumorigenesis, such as proliferation, invasion and drug resistance.

The upstream mechanisms regulating USP22 expression in cancer have been extensively studied. USP22 expression could be positively or negatively controlled at the transcriptional level. CREB appears to activate the transcription of USP22 in cancer cells [243]. Interestingly, c-Myc, a substrate of USP22 in breast cancer cells, could also promote the transcription of USP22, thus forming a positive feedback to stabilize another substrate SIRT1 to support leukemogenesis [244]. On the contrary, chemotherapy could activate p38 MAPK to diminished the expression of USP22 at the transcriptional level, thus inhibiting cervical cancer proliferation [245]. At the post-transcriptional level, USP22 is regulated by several miRNAs, including miRNA-30-5p, miRNA-29c, miRNA-101, and miRNA-34b. It has been shown that loss of these miRNAs leads to overexpression of USP22, thus promoting cancer stemness, proliferation, metastasis, chemoresistance among nasopharyngeal carcinoma, colorectal, pancreatic, lung and thyroid [246–251] cancers. Meanwhile, CD26 was also reported to also enhance the expression of USP22 and oncogenesis of malignant pleural mesothelioma [252]. Although limited mechanistic details regarding the regulation of enzymatic activity of USP22 are currently available, all these findings implicate a complex regulatory network that governs USP22 expression in cancer cells.

As aforementioned, although there are plenty of clinical and biochemical evidence suggesting that USP22 might serve as an oncogenic USP, a recent report has completely overturned these assumptions. Systemic *Usp22*$^{-/-}$ induces spontaneous generation of acute myeloid leukemia among KRAS-activated mice. Conversely, restoration of USP22 could rescue leukemogenesis and induce normal hematopoietic differentiation [253]. This hints that USP22 might play a tumor-suppressive role in the development of leukemia. Taken together, current evidence suggest that the actual neoplastic function of USP22 may vary between different cancer types, especially between solid and hematological malignancies. Therefore, genetically modified mouse models are needed to confirm whether USP22 is indeed oncogenic among solid

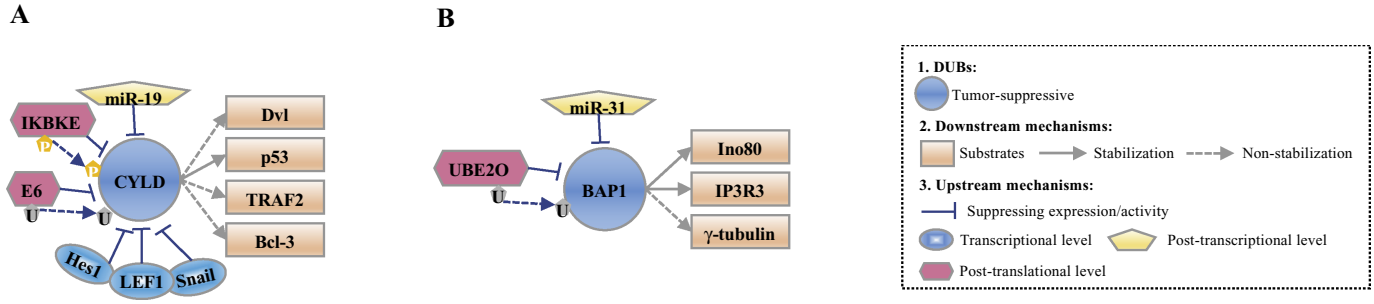


**Fig. 5.** Major downstream, upstream mechanisms of key tumor-suppressive DUBs.
A. CYLD; B. CSN5.

cancers (Fig. 6).

*2.1.3.3.5. USP28.* Compared to other counterparts, USP28 is a newly discovered member of context-dependent USPs. Conditional knockout of *Usp28* in gut epithelium ameliorates tumorigenesis and extends lifespan of $Apc^{min/+}$ mice [254], suggesting an oncogenic role in colorectal cancer development. However, systemic depletion of *Usp28* also increases susceptibility of liver carcinogenesis induced by diethylnitrosamine [255], which implicates that USP28 could also serve as a tumor suppressor. Consistent with the results from knockout mouse models, context-dependent clinical implications of USP28 have also been confirmed by pathological evidence. Overexpression of USP28 has been detected in multiple types of solid cancers, such as glioma [256], lung cancer [257] and bladder cancer [258], which also serve as a negative indicator of survival prognosis. However, USP28 is downregulated in melanoma [259] and breast cancer [255], which positively correlates to prognostic consequences (Table 5). Mechanistically, USP28 has been identified to target c-Myc [260], FBW7 [261], LIN28A [262], LSD1 [263], c-Jun [254], NICD1 [254] and p53 [264], most of which mediate the oncogenic role of USP28, with exception for p53 [264] (Tables 2 and 5). More importantly, both c-Myc [260] and c-Jun [254] are downstream transcriptional factors of the Wnt pathway, while NICD1 also acts as a receptor of Notch signaling [254], all of which ultimately result in oncogenic transcriptions among cancer cells. Additionally, c-Myc [260], c-Jun [254] and NICD1 [254] are also the substrates of E3 ligase FBW7, which itself is stabilized by USP28 [261], suggesting an overlapping and complicated regulatory network involving USP28 and FBW7 in cancer progression.

In terms of the upstream regulatory mechanisms of USP28 expression in cancer cells, different levels of regulations have been reported. HNF-1β could transcriptionally upregulate the expression of USP28, which subsequently enhance cell viability of ovarian clear cell carcinoma following exposure to genotoxic agents [265]. Meanwhile, c-Myc, the substrate of USP28, also functions as a transcriptional factor to elevate the expression of USP28 in colorectal cancer cells, thus forming a positive feedback loop [254]. At the post-transcriptional level, loss of miR-3940-5p leads to overexpression of USP28 in lung cancer cells [266]. Meanwhile, at the post-translational level, HDAC5 could directly interact with and inhibit the ubiquitylation level of USP28, which then promotes the protein stability of USP28 in breast cancer cells and subsequently triggers the upregulation of LSD1 and oncogenic transcriptions [267]. However, there is currently little knowledge about the upstream regulations on USP28 enzymatic activity as well as on the downregulated expression of USP28 in certain types of cancer cells. Overall, we believe that USP28 might play context-dependent role in neoplastic development based on the above-described evidence, although further pathological and biochemical studies are needed (Fig. 6).

Besides the aforementioned USPs, other members such as USP15 and USP44 may also play potential context-dependent role in cancer development (Table 5), suggesting that more in-depth investigations will help to shed light on their contributions in the future.

## 2.2. The OTU subfamily

### 2.2.1. Introduction of OTUs

A total of 16 OTU members have been identified in human genome, making them the second largest DUB subfamily. All members could be further divided into four subclasses, namely OTUB/Otubains, OTUD, A20-like, and OTULIN [268]. These four subclasses are mainly distinguished by the size of catalytic domains, where OTUD enzymes contain the smallest domain [18,268]. The molecular functions of OTUs are quite similar to that of USPs, despite their differences in recognizing linkage specificity [268]. OTUs regulate diverse cellular signaling cascades, which therefore play essential roles in mediating multiple physiological events such as embryogenesis [269], innate and adaptive immunity [270–272], hematopoiesis [273], neural development [274] and metabolic homeostasis [275]. Moreover, dysregulated OTUs have also been linked to various human diseases, including Parkinson's Disease [276], autoimmune disorders [277] and congestive heart failure [278]. OTUs likewise play a complex role in neoplastic development, which are discussed in the following chapters.

### 2.2.2. Physiological role of OTUs-evidence from knockout and transgenic mouse models

Based on the evidence from genetically-modified mouse models, OTUs have been linked to the regulation of multiple physiological events, especially embryonic growth, immune-inflammatory response, hematopoiesis, and cardiovascular homeostasis (Table 6).

Systemic or conditional deletion of several OTUs culminate in embryonic or early postnatal lethality, including *Otub1* [269], *Otu6B* [279] and *A20* [280,281], which might be attributed to defects in heart development, immune homeostasis and hematopoiesis respectively. These results suggest that OTUs might be critical for normal mammalian embryogenesis.

The regulatory role by OTUs in the immune response have been extensively investigated where different OTUs could play either an activating or suppressive role in immune regulations. OTUD1 [282], OTUD5 [283], A20 [284] and OTULIN [23] appear to serve as immune suppressors, since their depletion results in enhanced innate or adaptive immunity in response to pathological or autoimmune stimuli. For example, systemic [281] or conditional [285] deficiency of *A20* leads to systemic enhancement or conditional activation of immune-inflammatory responses in corresponding tissues. Specifically, global knockout of *A20* causes severe inflammation, cachexia, and multiple organ failure [281], while conditional ablation of *A20* in connective tissue mast cell [284], epidermis [286], intestinal epithelial cell [287] and microglia [288] lead to aggravated collagen-induced arthritis, exacerbated experimental psoriasis and atopic dermatitis, increased susceptibility to experimental colitis, as well as multiple sclerosis-like disease, respectively. Transgenic overexpression of *A20* in intestinal epithelial cells also results in resistance of DSS-induced colitis [289]. All these findings implicate widespread participation of A20 in inhibiting the immune response within diverse tissues. On the other side, OTUD4

**Table 5**
Major context-dependent USPs.

| USPs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Pathological evidence (cancer relevant human specimens) | Biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| USP8 | NA | **Overexpressed** in cervical cancer [643], lung cancer [644]; **Downregulated** in breast cancer [645] | **Oncogenic: Breast cancer:** Cx43 [539]; **Tumor-suppressive: Glioblastoma:** AIP4 [540] | Potential |
| USP9X | **Tumor-suppressive:** 1. Systemic *Usp9x*$^{-/-}$ increases tumor burden in colitis-associated colorectal cancer [195] | **Overexpressed** in oral squamous cell cancer [646], lung cancer [196], breast cancer [202], gastric cancer [647], melanoma [544], glioma [199], lymphoma [200], esophageal cancer [201], multiple myeloma [197]; **Downregulated** in colorectal cancer [195], pancreatic cancer [198] | **Oncogenic: Unspecified:** CLASPIN [541], pVHL [542]; **Breast cancer:** CEP131 [202], SMAD4 [543], SMURF1 [203], TDRD3 [210], TRB3 [211], YAP1 [204]; **Glioma:** β-catenin [199]; **Lung cancer:** TTK [196]; **Lymphoma:** MCL1 [197], XIAP [200]; **Melanoma:** Ets-1 [544]; **Prostate cancer:** IRS-2 [545]; **Tumor-suppressive: Colorectal cancer:** FBW7 [195]; **Kidney cancer:** AMOT [205]; **Pancreatic cancer:** Itch [198], LATS2 [206]; | Potential |
| USP10 | NA | **Overexpressed** in prostate cancer [217]; **Downregulated** in small intestinal cancer [215], liver cancer [213], lung cancer [214], gastric cancer [216], colon cancer [223], kidney cancer [221] | **Oncogenic: Unspecified:** Slug [219]; **Breast cancer:** TOP2α [218]; **Leukemia:** FLT3 [220]; **Prostate cancer:** G3BP2 [217]; **Tumor-suppressive: Colon cancer:** p53 [221], SIRT6 [223]; **Lung cancer:** MSH2 [222], p14ARF [546]; **Liver cancer:** AMPKα [213], PTEN [213]; | Potential |
| USP11 | NA | **Overexpressed** in liver cancer [648], lymphoma [549], breast cancer [547]; **Downregulated** in skin cancer [555] | **Oncogenic: Breast cancer:** XIAP [547]; **Colon cancer:** cIAP2 [548]; **Lymphoma:** eIF4B [549]; **Osteosarcoma:** RAE1 [550]; **Tumor-suppressive: Unspecified:** Mgl-1 [551], p21 [552]; **Glioma:** PML [553]; **Kidney cancer:** VGLL4 [554]; **Skin cancer:** XPC [555] | Potential |
| USP13 | NA | **Overexpressed** in ovarian cancer [558], lung cancer [558], glioblastoma [559]; **Downregulated** in breast cancer [563] | **Oncogenic: Unspecified:** MCL1 [558]; **Glioblastoma:** c-Myc [559]; **Ovarian cancer:** ACLY [560], OGDH [560], RAP80 [561]; **Melanoma:** MITF [562]; **Tumor-suppressive: Breast cancer:** PTEN [563] | Potential |
| USP15 | **Tumor-suppressive:** 1. Systemic *Usp15*$^{-/-}$ increases sensitivity to methylcholantrene-induced fibrosarcoma [495] | **Overexpressed** in multiple myeloma [649], lung cancer [566], glioblastoma [564] | **Oncogenic: Unspecified:** Mdm2 [90]; **Glioblastoma:** TβR-I [564]; **Liver cancer:** HBx [565]; **Lung cancer:** TOP2α [566]; **Tumor-suppressive: Unspecified:** Keap1 [567], p53 [568]; **Prostate cancer:** IRS-2 [569] | Potential |
| USP18 | **Oncogenic:** 1. Systemic *Usp18*$^{-/-}$ reduces mammary tumor growth [227]; 2. Systemic *Usp18*$^{-/-}$ reduces tumorigenicity of Kras-driven lung cancers [228]; 3. Conditional *Usp18*$^{-/-}$ mice are resistant to BCR-ABL–induced chronic myeloid leukemia [229]; **Tumor-suppressive:** 1. Systemic *Usp18*$^{-/-}$ induces spontaneous development of leiomyosarcoma [230] | **Overexpressed** in liver cancer [231], lung cancer [228] | **Oncogenic: Leukemia:** PML/RARα [232]; **Liver cancer:** BCL2L1 [231]; **Lung cancer:** KRAS [228] | Strong |
| USP20 | NA | **Overexpressed** in colon cancer [573]; **Downregulated** in gastric cancer [650] | **Oncogenic: Unspecified:** β-catenin [573]; **Tumor-suppressive: General:** CLASPIN [574]; **Leukemia:** Tax [575], TRAF6 [575] | Potential |
| USP21 | NA | **Overexpressed** in liver cancer [578], bladder cancer [576], **Downregulated** in kidney cancer [579] | **Oncogenic: Bladder cancer:** EZH2 [576]; **Liver cancer:** BRCA2 [577], MEK2 [578]; **Tumor-suppressive: Unspecified:** MARK1 [579] | Potential |
| USP22 | **Tumor-suppressive:** 1. Systemic *Usp22*$^{-/-}$ induces spontaneous generation of acute myeloid leukemia among KRAS-activated mice [253] | **Overexpressed** in malignant pleural mesothelioma [252], lung cancer [250], colorectal cancer [235], osteosarcoma [303], liver cancer [651], thyroid cancer [652], prostate cancer [653], cervical cancer [654], oral squamous cell cancer [655], salivary cancer [656], breast cancer [657] | **Oncogenic: Unspecified:** CCNB1 [95], CCND1 [580], FBP1 [581]; **Breast cancer:** c-Myc [582]; **Glioma:** KDM1A [542], BMI1 [539]; **Liver cancer:** SIRT1 [583]; **Lung cancer:** COX-2 [241], EGFR [240], H2A [242]; **Tumor-suppressive: Leukemia:** PU.1 [253] | Potential |
| USP24 | NA | **Overexpressed** in multiple myeloma [481]; **Downregulated** in lung cancer [585] | **Oncogenic: Lung cancer:** β-TrCP [584]; **Multiple myeloma:** Mcl-1 [481]; **Tumor-suppressive: Lung cancer:** Bax [585], E2F4 [585], p300 [585], securing [585] | Potential |
| USP26 | NA | NA | **Oncogenic: Prostate cancer:** AR [586]; **Tumor-suppressive: Glioblastoma:** SMAD7 [587] | Less potential |
| USP28 | **Oncogenic:** 1. Conditional *Usp28*$^{-/-}$ameliorates tumorigenesis and extends lifespan among Apc$^{min/+}$ mice [254]; **Tumor-suppressive:** 1. Systemic *Usp28*$^{-/-}$ increases susceptibility of liver carcinogenesis induced by diethylnitrosamine [255] | **Overexpressed** in glioma [256], lung cancer [257], colorectal cancer [254,260], bladder cancer [258], gastric cancer [310], esophageal cancer [658]; **Downregulated** in melanoma [259], breast cancer [255] | **Oncogenic: Unspecified:** c-Myc [260], Fbw7 [261], LIN28A [262]; **Breast cancer:** LSD1 [263]; **Colorectal cancer:** c-Jun [254], NICD1 [254]; **Tumor-suppressive: Unspecified:** p-53 [264] | Strong |
| USP29 | NA | NA | **Oncogenic: Unspecified:** Claspin [589]; **Tumor-suppressive: Unspecified:** p53 [590] | **Less potential** |

(*continued on next page*)

**Table 5** (*continued*)

| USPs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Pathological evidence (cancer relevant human specimens) | Biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| USP37 | NA | **Overexpressed** in breast cancer [659], lung cancer [602]; **Downregulated** in medulloblastoma [603] | **Oncogenic: Unspecified:** 14–3-3γ [600]; **Leukemia:** PLZF/RARA [601]; **Lung cancer:** c-Myc [602]; **Tumor-suppressive: Medulloblastoma:** p27 [603] | Potential |
| USP42 | NA | **Overexpressed** in gastric cancer [660] | **Tumor-suppressive: Unspecified:** p53 [605] | Less potential |
| USP44 | **Tumor-suppressive:** 1. Systemic *Usp44*$^{-/-}$ develops spontaneous tumors, especially lung cancer [507] | **Overexpressed** in glioma [607], gastric cancer [661], leukemia [662]; **Downregulated** in lung cancer [507] | **Oncogenic: Breast cancer:** H2B [606]; **Glioma:** securin [607] | Potential |
| USP46 | NA | **Downregulated** in colorectal cancer [609] | **Oncogenic: Cervical cancer:** Cdt2 [608]; **Tumor-suppressive: Colorectal cancer:** PHLPP [609] | Less potential |

Note: Based on different credibility of biological evidence, if the context-dependent role of one USP is confirmed by genetically-modified mouse models (must containing both oncogenic and tumor-suppressive models), then the evidence grade is strong. Potential grade is designated to those having both oncogenic and tumor-suppressive pathological evidence or one genetically-modified evidence plus one pathological evidence. Otherwise, the grade is designated as less potential under the remaining circumstances.

and TRABID may normally play an activating role in immune regulation, since the depletion of which results in increased susceptibility to lethal viral infection [290], as well as resistance to central nervous inflammation and experimental autoimmune encephalomyelitis [277], respectively. Nonetheless, unlike aforementioned OTUs, OTUD7B seems to play a controversial role in managing innate and adaptive immunity, where *Otud7BTUD7B*-null mice feature less T-cell activity and restricted autoimmune responses [291] while hyperactivity of B cell function as well as enhanced innate host-defense ability [292]. Taken together, these evidences suggest a critical and complex role for OTUs members in immune regulation.

OTUs also influence hematopoietic development and cardiac functionalities. Conditional deletion of *A20* in hematopoietic stem cells results in pathological hematopoiesis including anemia, lymphopenia, splenomegaly and hepatomegaly [280], while systemic or heart-specific transgenic expression of *A20* restores to cardiovascular defects in atherosclerosis [293], cardiac hypertrophy and fibrosis [278], and left ventricular dysfunction and compensatory hypertrophy after myocardial infarction [294].

### *2.2.3. Neoplastic role of OTUs-evidence from knockout and transgenic mouse models, clinical specimens and biochemical interactions*

*2.2.3.1. Oncogenic OTUs.* There are only two OTU members displaying potential oncogenic traits, both of which have limited confirmatory evidence from genetically modified mouse models. Overexpression of OTUB2 and OTUD2 have been identified in clinical specimens from breast [295] and liver [296] cancer, respectively (Table 8). Mechanistically, their oncogenic roles are mediated by deubiquitylation and stabilization of downstream substrates including YAP/TAZ and ITCH, which is linked to Hippo-independent [295] and Hippo-dependent [296] oncogenic transcription, respectively (Tables 7 and 8). Although poly-SUMOylation on OTUB2 is critical for its binding to and activation of YAP/TAZ, other regulatory events, especially the upstream mechanisms for both OTUs in cancer progression, are less extensively studied [295]. Therefore, further studies, especially using mouse genetic model studies, are warranted to pinpoint their physiological roles in tumorigenesis.

*2.2.3.2. Tumor suppressive OTUs.* Several OTUs demonstrate at least potential tumor suppressive activity, including OTUD1, OTUD5 and OTUD7A/Cezanne2 (Table 9).

Detection of cancer tissues in hepatocellular carcinoma (HCC) show that the expression of OTUD7A/Cezanne2 is also downregulated in liver cancer, whose anti-tumor role may be related to the deubiquitylation and stabilization of its substrate TRAF6 [297] (Tables 7 and 8). OTUD1 and OTUD5 may also have a potential tumor suppressive function. Unlike OTUD3, a context-dependent OTU which will be mentioned in the next part, limited data from genetically modified mouse models or pathological samples is available for the anti-tumor functions of OTUD1 and OTUD5, although these two OTUs are reported to stabilize tumor suppressive substrates, such as p53 [298,299] (Tables 7 and 8).

*2.2.3.3. Context-dependent OTUs.* Accumulating evidence have suggested that majority of the OTUs DUBs appear to play a context-dependent role in tumorigenesis, especially OTUB1, OTUD3, A20 and OTUD7B (Table 9).

*2.2.3.3.1. OTUB1.* Although there is a lack of evidence from genetically-modified mouse models, OTUB1 appears to play a tissue-specific role in tumorigenesis. Pathological evidence suggests that overexpression of OTUB1 has been observed in a variety of solid cancers, such as breast [300], lung [59], ovarian [301], glioma [302], liver [303] and colorectal [304] cancers. OTUB1 also serves as a negative prognostic indicator amid patients with those cancers (Table 9). Nonetheless, there is no pathological evidence concerning the anti-tumor role of OTUB1 described to date. Currently, context-dependent effects of OTUB1 on tumorigenesis is based mainly on a

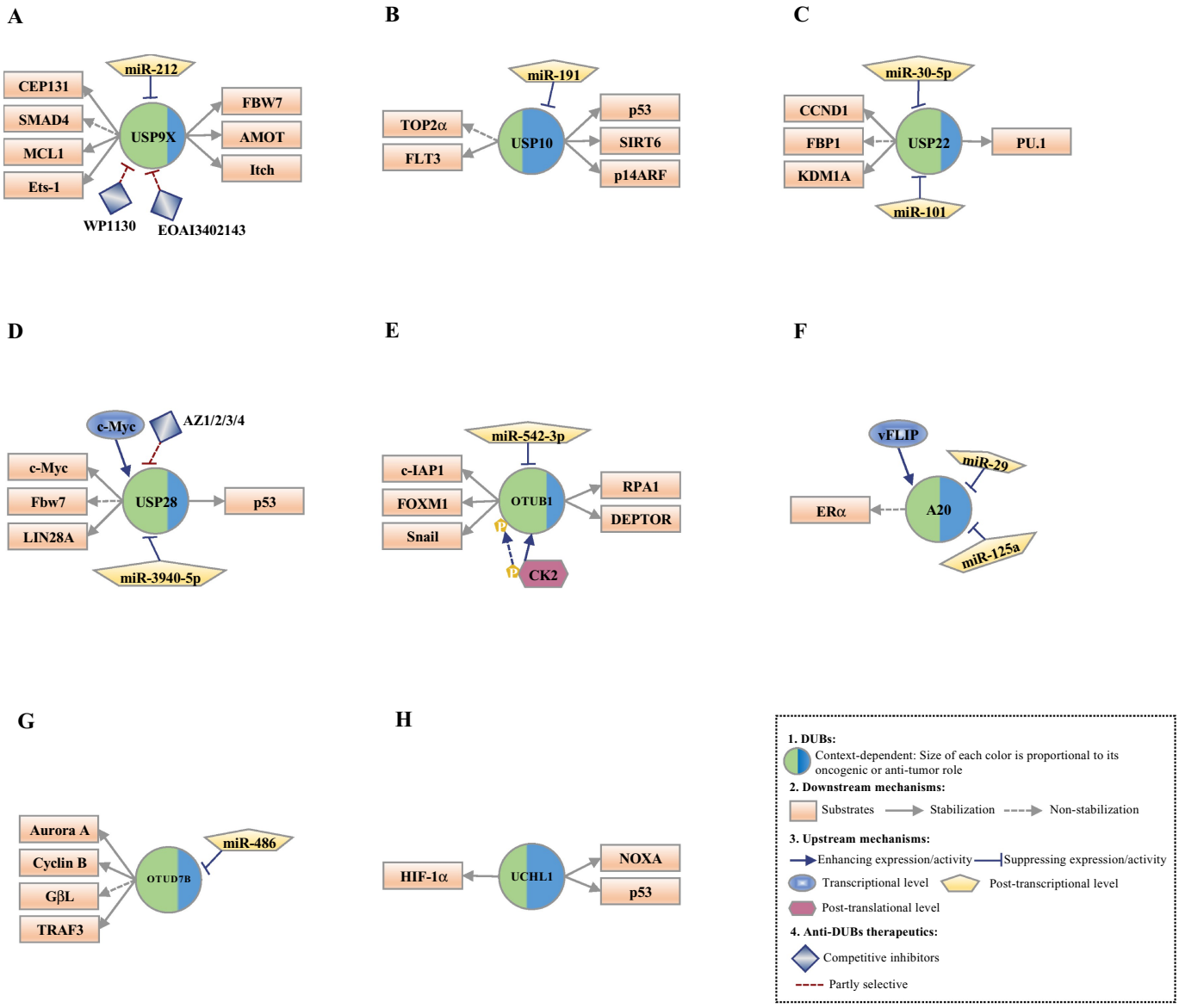


**Fig. 6.** Major downstream, upstream mechanisms as well as inhibitors of key context-dependent DUBs.
A. USP9X; B. USP10; C. USP22; D. USP28; E. OTUB1; F. A20; G. OTUD7B; H. UCHL1.

result of biochemical evidence, since OTUB1 could manage the deubiquitylation and stabilization of both oncogenic and tumor suppressive substrates under specific circumstances (Tables 7 and 9). With regard to its oncogenic potential, OTUB1 stabilizes c-IAP1, FOXM1, Snail and SLC7A11, leading to the activation of oncogenic MAPK pathway [305], acquired genotoxic resistance [300], epithelial-mesenchymal transition [306] and inactivation of tumor-related ferroptosis [307,308]. On the other hand, in terms of its tumor-inhibitory effects, through deubiquitylating RPA1, DEPTOR and ERα, OTUB1 could also promote PTEN tumor-suppression function [309], inhibition of mTORC1 activity and suppression of cell proliferation in cervical and endometrial cancer [310] [311], respectively.

With regard to the upstream regulatory mechanisms of OTUB1, miR-542-3p is reported to target and inhibit OTUB1, leading to the inhibition of colorectal cancer cell proliferation [312]. Meanwhile, CK2 could phosphorylate OTUB1 at Ser16 to trigger its nuclear localization and catalytic activity, thus facilitating DNA damage repair in osteosarcoma cells upon ionizing radiation [32]. Overall, OTUB1 may play a context-dependent role in malignancies from different tissues. However, more credible and strong evidence, especially genetically-modified mouse models, are required to further verify its neoplastic contributions (Fig. 6).

*2.2.3.3.2. OTUD3.* OTUD3 displays a tumor-suppressive role in a ubiquitously expressed transgenic mouse model, in which ectopic expression of OTUD3 results in decreased susceptibility of breast tumorigenesis [313], while knockout of *Otud3* in mouse models results in increased susceptibility of breast cancer [314]. Meanwhile, downregulated expression of OTUD3 has also been discovered in breast cancer, hepatocellular cancer, colon cancer and cervical cancer specimens [313,314], and OTUD3 serves as a positive prognostic indicator among breast cancer patients as well [313] (Table 9). Additionally, loss-of-function mutations of OTUD3 have been detected in multiple types of human cancers including breast cancer [313], further supporting a likely tumor-suppressive role of OTUD3. As for the downstream regulatory mechanisms, PTEN [313] and TOP2A [315] could be deubiquitylated and stabilized by OTUD3, which subsequently leads to tumor-inhibitory events (Tables 7 and 9). Nevertheless, little is currently known regarding the upstream regulatory mechanisms controlling the activity or expression level of OTUD3 in the cancer setting.

**Table 6**
Major phenotypes of OTUs knockout and transgenic mice.

| Gene | Mode | Phenotypic alterations | |
|---|---|---|---|
| | | Cancer-relevant | Cancer-irrelevant |
| *Otub1*$^{-/-}$ | Systemic | NA | **Embryogenic:** Embryonic lethality [269] |
| *Otud1*$^{-/-}$ | Systemic | NA | **Immune:** More resistant to RNA virus infection [282] |
| *Otud2* (transgenic) | Conditional (hepatocyte) | NA | **Digestive:** Hepatomegaly due to enhanced proliferation of hepatocytes [296] |
| *Otud3* (transgenic) | Systemic | **Breast cancer:** Less prone to tumorigenesis [313]<br>**Lung cancer:** More susceptible to Kras$^{G12D}$-drivern lung tumorigenesis [314] | **Embryogenic:** Reduced whole body size and smaller organs [313] |
| *Otud3*$^{-/-}$ | Systemic | **Breast cancer:** more prone to tumorigenesis [314]<br>**Lung cancer:** resistant to Kras$^{G12D}$-drivern lung tumorigenesis [314] | NA |
| *Otud4*$^{-/-}$ | Systemic | NA | **Immune:** Increased susceptibility to lethal viral infection [290] |
| *Otud5*$^{-/-}$ | Conditional (T-cell) | NA | **Immune:** Exacerbated inflammation in the small intestine after challenge with anti-CD3 antibodies [283] |
| *Otud6b*$^{-/-}$ | Systemic | NA | **Embryogenic:** Perinatal lethality with smaller body size and congenital heart defects [279] |
| *A20*$^{-/-}$ | Systemic | NA | **Immune:** Neonatal lethality with severe systemic inflammation, cachexia and multiple organ failure [281] |
| *A20*$^{-/-}$ *A20* (transgenic) | Conditional (airway epithelial cell) | NA | **Immune:** Resistant to influenza A virus infection [285] |
| | Conditional (B cell) | NA | **Immune:** Prone to food allergy [663]; Hyperactivation, impaired differentiation and enhanced proliferation of B cells, causing inflammation and autoimmunity [270–272] |
| | Conditional (connective tissue mast cell) | NA | **Immune:** Aggravated collagen-induced arthritis and enhanced allergic airway inflammation [284] |
| | Conditional (dendritic cell) | NA | **Immune:** Spontaneous inflammation among parenchymatous organs while higher lethality following low dose of LPS [664]; Spontaneous development of lymphocyte-dependent colitis, seronegative ankylosing arthritis and enthesitis conditions stereotypical of human inflammatory bowel disease [665]; Spontaneous maturity and hyperactivation of dendritic cells, as well as development of systemic autoimmunity [666] |
| | Conditional (epidermis) | NA | **Dermal:** Ectodermal organ abnormalities, including disheveled hair, longer nails and sebocyte hyperplasia due to keratinocyte hyperproliferation [667]; Exacerbated disease severity upon induction of experimental psoriasis, atopic dermatitis, or skin barrier disruption due to increased skin inflammation [286] |
| | Conditional (endothelial cell) | NA | **Immune:** Uncontrolled lung vascular leak and persistent sequestration of polymorphonuclear neutrophil after LPS challenge [668] |
| | Conditional (group 2 innate lymphoid cell) | NA | **Immune:** Promoting adaptive small-intestinal lengthening and remodeling [669] |
| | Conditional (hematopoietic stem cell) | NA | **Hematopoietic:** Postnatal lethality with pathological hematopoiesis including anemia, lymphopenia, splenomegaly and hepatomegaly [280] |
| | Conditional (hepatocyte) | NA | **Digestive:** Exacerbated nonalcoholic fatty liver disease- and nonalcoholic steatohepatitis-related phenotypes [275] |
| | Conditional (intestinal epithelial cell) | NA | **Immune:** Increased susceptibility to experimental colitis [287] |
| | Conditional (intestinal epithelial cell and myeloid cell) | **Colorectal cancer:** Development of colorectal cancer among aged mice [316] | **Immune:** Spontaneous development of intestinal inflammation and epithelial defects [316] |
| | Conditional (liver parenchymal cell) | **Liver cancer:** Increased susceptibility to chemically or high fat-diet-induced hepatocellular carcinoma development [317] | **Immune:** Spontaneous development of chronic liver inflammation and steatosis [317] |
| | Conditional (microglia) | NA | **Nervous:** Massive microglia activation, neuroinflammation, and lethality after administration of sublethal dose of lipopolysaccharide, increased microglial cell number, altered neuronal synaptic function as well as exacerbated multiple sclerosis-like disease [288] |
| | Conditional (multipotent progenitor) | NA | **Hematopoietic:** Modest changes in hematopoiesis with alterations in hematopoietic stem and progenitor cell pool, as well as loss of hematopoietic stem quiescence and compromised long-term hematopoietic reconstitution [273] |
| | Conditional (myeloid cell) | NA | **Immune:** Spontaneous development of erosive polyarthritis resembling rheumatoid arthritis as well as promoted osteoclastogenesis [670]; Resistant to influenza A virus infection [671] |
| | Conditional (neuroectodermal cell) | NA | **Immune:** Severer experimental autoimmune encephalomyelitis [672] |
| | Conditional (T-cell) | NA | **Immune:** Quantitatively enlarged thymic and peripheral Treg cell compartments [673]; Less graft-versus-host disease after |

(*continued on next page*)

**Table 6** (*continued*)

| Gene | Mode | Phenotypic alterations | |
|---|---|---|---|
| | | Cancer-relevant | Cancer-irrelevant |
| | | | conventional allogeneic hematopoietic stem cell transplantation [674]; Impaired pathogen control in primary but improved clearance in secondary infection with *Listeria monocytogenes* [675]; Impaired NKT cell development [676]; Lymphadenopathy and infiltration of T-cells in peripheral organs [677] |
| | Systemic | NA | **Immune:** Highly susceptible to TNF-induced intestinal epithelial cell apoptosis, bowel damage, shock and lethality [678]; **Cardiovascular:** Less atherosclerotic lesion development [293] |
| *A20* (transgenic) *Otud7b*$^{-/-}$ | Conditional (heart) | NA | **Cardiovascular:** Attenuated pathological cardiac hypertrophy and fibrosis [278]; Improved left ventricular performance and reduced compensatory hypertrophy after myocardial infarction [294] |
| | Conditional (hepatocyte) | NA | **Digestive:** Blocked onset and progression of nonalcoholic fatty liver disease [275] |
| | Conditional (intestinal epithelial cell) | NA | **Immune:** Resistant to DSS-induced colitis [289] |
| | Systemic | **Lung cancer:** Inhibited initiation and progression of Kras-driven lung cancer [335] | **Immune:** Lower number of T-cells, reduced T-cell response to bacterial infections and ameliorated pathogenesis of T-cell dependent autoimmunity [291]; B cell hyper-responsiveness to antigens, lymphoid follicular hyperplasia in the intestinal mucosa, and elevated host-defense ability against Citrobacter rodentium [292] |
| *Trabid*$^{-/-}$ | Systemic | NA | **Immune:** Resistant to central nervous inflammation and experimental autoimmune encephalomyelitis [277] |
| *Otulin*$^{-/-}$ | Conditional (immune cell) | NA | **Immune:** Spontaneous and severe acute systemic inflammation characterized by rapid weight loss, increased levels of pro-inflammatory cytokines in serum, neutrophilia with all the hallmarks of emergency granulopoiesis and infiltration of neutrophils into multiple tissues [23] |

Although studies on *Otud3* transgenic and knock-out mouse models show OTUD3 is a tumor suppressor in breast cancer, OTUD3 may also acts as a tumor promoting factor since *Otud3* transgenic mice are more prone to develop Kras$^{G12D}$ driven lung cancer while *Otud3* knock-out mice display lower cancer susceptibility in Kras$^{G12D}$-driven lung cancer [314]. Clinical investigation found the expression level of OTUD3 is upregulated in lung adenocarcinoma and unconnected to the expression level of PTEN, whose expression is downregulated in lung adenocarcinoma. Furthermore, lung cancer patients with relatively high levels of OTUD3 show poorer overall survival [314]. Mechanistically, OTUD3 deubiquitylates and stabilizes GRP78 (also called BiP, a well-known protein in the ER stress response) to promote lung cancer cell proliferation, wheras the interaction between OTUD3 and PTEN does not appear to have functional relevance as it does in other tissues [314]. Therefore, the tumorigenesis promoting or suppressive function of OTUD3 likely depends on the cell/tissue context-dependent functions of its substrates (Table 9).

*2.2.3.3.3. A20*. A20, also known as TNFAIP3, is by far the most well-understood member of OTUs in both neoplastic and non-neoplastic settings. Conditional knockout of *A20* in intestinal epithelial cells and hepatocytes induce development of colorectal cancer in aged mice [316] and increase susceptibility to chemically or high fat-diet-induced hepatocellular carcinogenesis [317], suggesting a tumor-protective role of A20 in these tissues. However, clinical pathological evidence suggests a contradictory result among different types of cancer (Table 9). A20 is overexpressed in both solid and hematological malignancies, such as breast cancer [62], esophageal cancer [318], leukemia [319,320] and glioma [321], where A20 is a negative indicator of patient prognosis. Conversely, A20 is downregulated in a wide spectrum of malignant neoplasms, such as nasopharyngeal cancer, where lower A20 expression correlates to worse survival [322]. With respect to its downstream substrates, unlike other OTUs, only ERα [323] is included as a cancer relevant substrate. It is likely that A20 could function as either DUB or E3 ligase, those cancer-irrelevant DUB or E3 ligase substrates such as RIP1 [324] account for the majority of A20 substrate family. Through deubiquitylating and stabilizing ERα, A20 could enhance the proliferation of endometrial cancer cells [323] to play an oncogenic role (Tables 7 and 9).

Contrary to the limited reports on its downstream mechanisms, the upstream regulatory mechanisms of A20 in cancer progression have been well described. At the transcriptional level, vFLIP oncoprotein from Kaposi's sarcoma-associated herpesvirus could transcriptionally activate *A20*, leading to the development of Kaposi's sarcoma [325]. At the post-transcriptional level, many miRNAs inhibit the expression of A20 in order to subdue its tumor-suppressive role in cancer progression, such as miR-125a in diffuse large B-cell lymphoma [326], miR-29 in sarcoma [327] and miR-125b in nasopharyngeal carcinoma [322]. Moreover, TNFα [328] and FGFR1 [329] are able to upregulate the expression of A20 among breast cancer cells while DEPDC1 could downregulate A20 in nasopharyngeal carcinoma [330] to trigger cancer progression, despite a lack of further mechanistic insights. A20 might also be inactivated by somatic mutations, where its loss-of-function mutation or deletion could trigger oncogenesis of Hodgkin and non-Hodgkin lymphomas [331–334]. Therefore, A20 appears to be a potential context-dependent OTU in diverse malignancies (Fig. 6).

*2.2.3.3.4. OTUD7B*. OTUD7B, also called Cezanne, is another vital context-dependent OTU in neoplastic regulations. Pro-tumorigenic role of OTUD7B has been demonstrated by the finding that global knockout of *Otud7B* inhibits the initiation and progression of KRAS-driven lung cancer [335]. However, pathological evidence from human samples appears to be inconsistent with this conclusion. OTUD7B is overexpressed only in breast cancer where it serves as a negative prognostic indicator [336], while OTUD7B is downregulated in liver cancer [337] and glioma [338] and serves as a favorable prognostic marker (Table 9). The identification of downstream substrates of OTUD7B also supports an oncogenic role. Specifically, stabilization of Aurora A [339] and Cyclin B [339] by OTUD7B-mediated deubiquitylation leads to mitotic progression and cancer cell proliferation. Moreover, deubiquitylation of EGFR [336] and GβL [335] facilitates the activation of EGF and mTOR signaling, respectively, which subsequently promotes breast and lung cancer progression (Tables 7 and 9). Recently, OTUD7B has been

demonstrated to deubiquitylate and stabilize Sox2, a core transcriptional factor in stem cells, and maintain the stemness of neural progenitor cells. In this regard, OTUD7B antagonizes the effect of Cullin4A-DET1-COP1 ubiquitin ligase on Sox2 and contributes to the homeostatic control of stem cell differentiation [340]. Given that Sox2 is a potential oncogenic factor, we propose that OTUD7B might also play a pro-tumorigenic role in neuroblastoma development.

In terms of upstream regulatory mechanisms, OTUD7B is reported to be targeted by several miRNAs including miR-1180, miR-500 and miR-486, leading to activation of NF-κB signaling and progression of liver cancer [341], gastric cancer [342] and glioma [338], respectively. Nevertheless, there is currently little knowledge about the transcriptional or post-translational control on OTUD7B expression or activity, which warrants further investigation. Taken together, although the oncogenic activity of OTUD7B seems to be predominant, we still cannot rule out its anti-tumor role in certain types of cancer. Therefore, we suggest that OTUD7B might act as a potential context-dependent OTU (Fig. 6).

## 2.3. UCHs

### 2.3.1. Introduction of UCHs

Unlike USPs and OTUs, the UCH subfamily only consists of four members, namely UCHL1, UCHL3, UCHL5 and BAP1 [18,343]. Each member of the UCH DUBs features a C12 peptidase domain formed by a knotted peptide backbone at its N-terminus, an extension at its C-terminus as well as an unstructured loop mediating the access of the substrate to catalytic site [343]. Similar to the majority of DUB members, UCH DUBs also regulate multiple physiological processes, such as embryonic development [344], neurogenesis [345], metabolic homeostasis [346], urinary development [347] and reproduction [348]. On the contrary, disrupted function of UCHs in mammalian cells lead to multiple disorders, such as Parkinson's Disease [26] and cancer [349], which is discussed in following chapters.

### 2.3.2. Physiological role of UCHs-evidence from knockout and transgenic mouse models

Based on genetically modified mouse models, UCHs have been implicated in various physiological events, especially neurogenesis, urinary homeostasis and reproductive regulations (Table 10). Both UCHL1 and UCHL3 are closely linked to neural development, where systemic deletion results in neurodegeneration in the central and peripheral nervous system, leading to neuromuscular disorder [345], learning defects [350], early-stage retinal degeneration [351] and retinal neuronal dysfunction [352]. Meanwhile, global knockout of *Uchl1* causes diverse urinary pathologies, including hyperphosphatemia, phosphaturia [353], proteinuria, urine retention and hypotension [347]. Conditional ablation of *Bap1* also leads to neonatal kidney dysfunction and subsequent lethality [354]. As for the reproductive involvement, either systemic deletion [355] or transgenic expression [348] of *Uchl1* leads to male sterility by compromising normal spermatogenesis, indicating that a specific level of UCHL1 is critical for spermatogenesis. Conditional knockout of *Uchl1* in the ovum also significantly increases the rate of polyspermy and reduces litter size [356]. Furthermore, UCHs have also been linked to embryonic development and hematopoiesis, since the deletion of *Bap1* culminates in embryonic lethality [344] and abnormal hematopoiesis [357].

### 2.3.3. Neoplastic role of UCHs-evidence from knockout and transgenic mouse models, clinical specimens and biochemical interactions

#### 2.3.3.1. Oncogenic UCHs

*2.3.3.1.1. UCHL5.* Although there is no evidence from genetically engineered mouse models, the oncogenic role of UCHL5 can be implicated from multiple pathological and biochemical evidence. UCHL5 is overexpressed in both solid and hematological malignancies, including ovarian [358], liver [359], esophageal cancers [360] and multiple myeloma [141] (Table 12). Consistently, higher level of UCHL5 correlates with poor prognosis among patients with esophageal [360], liver [359] and ovarian [358] cancers. As for its downstream mechanisms, three major substrates have been verified to

**Table 7**
Major cancer-relevant substrates of OTUs.

| OTUs | Substrates | Modifications | Major neoplastic consequences |
|---|---|---|---|
| OTUB1 | c-IAP1 | Stabilization | Possible role in activating oncogenic MAPK pathway [305] |
| | FOXM1 | Stabilization | Enhanced proliferation and epirubicin resistance of breast cancer cells [300] |
| | Snail | Stabilization | Promoting metastasis of esophageal cancer [306] |
| | SLC7A11 | Stabilization | Promoting cancer growth via mediating ferroptosis [308] |
| | RPA1 | Stabilization | Promoting PTEN-involved tumor-suppressive response [309] |
| | DEPTOR | Stabilization | Inhibition on mTORC1 activity and reduced proliferation of cervical cancer cells [310] |
| | ERα | Altered activity | Suppression on ERα-mediated oncogenic transcription on endometrial cancer cells [311] |
| OTUB2 | YAP/TAZ | Stabilization | Promoting breast cancer metastasis [295] |
| OTUD1 | p53 | Stabilization | Possible role in inducing cell cycle arrest and apoptosis among cancer cells [298] |
| | YAP | Subcellular localization | Possible growth-inhibitory function in cancer cells [679] |
| | SMAD7 | Stabilization | Inhibition of stemness and metastasis of breast cancer cells [680] |
| OTUD2 | ITCH | Stabilization | Contributing to liver carcinogenesis [296] |
| OTUD3 | PTEN | Stabilization | Inhibition on breast cancer progression [313] |
| | TOP2A | Stabilization | Promoting PTEN-involved tumor suppressive events [315] |
| | GRP78 | Stabilization | Contributing to lung tumorigenesis [314] |
| OTUD5 | p53 | Stabilization | Possible role in inducing apoptosis among cancer cells [299] |
| | PDCD5 | Stabilization | Increased sensitivity to genotoxic agents among cancer cells [681] |
| | UBR5 | Stabilization | Possible role in maintaining genomic stability and cancer suppression [682] |
| A20 | ERα | Stabilization | Enhancing proliferation of endometrial cancer cells [323] |
| OTUD7B (Cezanne) | Aurora A | Stabilization | Mitotic progression and cancer cell proliferation [339] |
| | Cyclin B | Stabilization | Mitotic progression and cancer cell proliferation [339] |
| | EGFR | Stabilization | Promoting breast cancer progression [336] |
| | GβL | Altered activity | Promoting lung cancer initiation and progression [335] |
| | Sox2 | Stabilization | Possible role in promoting tumorigenesis of neuroblastoma [340] |
| | TRAF3 | Stabilization | Possible role in promoting tumorigenesis of neuroblastoma [683] |
| OTUD7A (Cezanne2) | TRAF6 | Altered activity | Anti-tumor effects on liver carcinogenesis [297] |
| TRABID | EZH2 | Stabilization | Promoting breast cancer development [275] |
| | Twist1 | Altered activity | Inhibiting liver cancer progression [275] |

Note: Substrates should directly interact with and then be deubiquitylated by its corresponding DUBs based on the catalytic enzymatic functions. Those feature non-catalytical interactions or deubiquitylation by DUBs should not be considered as substrates.

**Table 8**
Major oncogenic and tumor-suppressive OTUs.

| OTUs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Major pathological evidence (cancer relevant human specimens) | Major biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| **Oncogenic** | | | | |
| OTUB2 | NA | **Overexpressed** in breast cancer [295] | **Breast cancer:** YAP/TAZ [295] | Potential |
| OTUD2 | NA | **Overexpressed** in liver cancer [296] | **Liver cancer:** ITCH [296] | Potential |
| **Tumor-suppressive** | | | | |
| OTUD1 | NA | NA | **Unspecified:** p53 [298], YAP [679]; **Breast cancer:** SMAD7 [680] | Less potential |
| OTUD5 | NA | NA | **Unspecified:** p53 [299], PDCD5 [681], UBR5 [682] | Less potential |
| OTUD7A (Cezanne2) | NA | **Downregulated** in liver cancer [297] | **Liver cancer:** TRAF6 [297] | Potential |

Note: Based on different credibility of biological evidence, if the oncogenic or tumor-suppressive role of one OTU is confirmed by genetically-modified mouse models, then the evidence grade is strong. Otherwise, the grades are designated as potential and less potential in terms of pathological and biochemical evidence respectively.

contribute to the oncogenic function of UCHL5 under different circumstances. The stabilization of TGFBR1 [361] and PRP19 [359] affects TGF-β signaling and spliceosome-related DNA segregation and damage, respectively, therefore contributing to oncogenic transformation. Meanwhile, the deubiquitylation on Tcf7 by UCHL5 could alter its activity and subsequently activate the oncogenic Wnt pathway in liver cancer cells [362] (Tables 11 and 12). Nonetheless, with limited knowledge on the upstream regulatory mechanisms of the UCHL5, further studies are needed to fully dissect the exact role of UCHL5 in tumorigenesis (Fig. 4).

Apart from UCHL5, UCHL3 also displays potential oncogenic functions, given that it is overexpressed in breast cancer [363] and has been shown to deubiquitylate and stabilize TDP1 to enhance drug insensitivity in rhabdomyosarcoma cells [364].

#### 2.3.3.2. Tumor-suppressive UCHs

*2.3.3.2.1. BAP1.* As the most extensively investigated member of the UCHs, BAP1 is widely known for its tumor suppressive functions in various malignancies [365]. Both systemic knockout and conditional deletion of *Bap1* in hematopoietic cells induce malignant myeloid transformation in adult mice [344]. Meanwhile, BAP1 is downregulated in different kinds of cancers, especially in melanoma [366], malignant mesothelioma [367], kidney [368] and gastric [369] cancer, and serves as a favorable prognostic factor (Table 12). Multiple downstream substrates mediate the anti-tumor effects of BAP1 in various cancers. By deubiquitylating Ino80 [370], γ-tubulin [371] and MCRS1 [372], BAP1 enhances DNA stability and inhibits malignant transformation in breast and kidney cancer. Additionally, stabilization of IP3R3 also triggers calcium release from the endoplasmic reticulum into the cytosol and mitochondria, which induces cell apoptosis to inhibit tumorigenesis [373]. Moreover, deubiquitylation of H2A by BAP1 [374] leads to multiple transcriptional alterations in metabolic genes, thus linking the metabolic regulatory network to tumor suppression [375,376] (Tables 11 and 12).

The upstream mechanisms regulating BAP1 expression or activity have also been widely studied. miRNA-31 lowers the expression levels of BAP1 in both lung [377] and cervical [378] cancer cells, which subsequently contributes to tumor growth. The catalytic activity of BAP1 is stimulated by its interaction with ASXLs to enable its tumor suppressive function [379]. Moreover, auto-deubiquitylation prevents BAP1 from cytoplasmic sequestration induced by ubiquitin ligase UBE2O in cancer cells, which helps to maintain its tumor suppressive transcriptional functionality [34]. In addition, apart from the upstream mechanisms, loss-of-function mutations are also a major cause of the BAP1 deficiency in multiple cancers, especially leukemia [344], uveal melanoma [380,381], malignant mesothelioma [382], intrahepatic cholangiocarcinoma [383,384] and renal cell carcinoma [385,386]. Overall, we strongly believe that BAP1 acts as a key tumor-suppressor in a variety of malignancies (Fig. 5).

#### 2.3.3.3. Context-dependent UCHs

*2.3.3.3.1. UCHL1.* UCHL1 appears to play a context-dependent role in various cancers. Experimental evidence from genetically modified mouse models support an oncogenic role of UCHL1, since systemic deletion of *Uchl1* results in significant resistance to Myc-induced lymphomas [387] while transgenic expression of *Uchl1* leads to increased susceptibility to development of spontaneous lymphoma and lung cancer [388]. However, pathological evidence suggests that UCHL1 may either play an oncogenic or tumor suppressive role in distinct tumors of tissue origin. UCHL1 is overexpressed in breast [389] and lung cancer [390] and in osteosarcoma tissues [391], but downregulated in the majority of cancer types such as nasopharyngeal cancer [392], melanoma [393] and colorectal cancer [393] (Table 12). Consistently, higher expression of UCHL1 indicates worse survival in breast cancer [389] and osteosarcoma [391], while better clinicopathological features in kidney cancer [394] despite a lack of prognostic results.

Several substrates have been confirmed to mediate the downstream biological functions of UCHL1 in tumorigenesis. For example, UCHL1 stabilizes HIF-1α to promote cancer cell metastasis [395], while on the contrary, deubiquitylate and stabilizes NOXA [393] and p53 [392] to enhanced chemo-sensitivity and tumor suppression in nasopharyngeal cancer [392] (Tables 11 and 12). In spite of limited evidence to pinpoint its exact substrate, UCHL1 is found to activate eIF4F [387], MAPK [389] and AKT [388] signaling pathways, therefore contributing to the oncogenesis of lymphoma and breast cancer. Unfortunately, there is limited understanding of the context-dependent role of UCHL1 in tumorigenesis, which warrants further in-depth studies (Fig. 6).

### 2.4. Josephins

#### 2.4.1. Introduction and physiological role of Josephins

Like UCHs, Josephins is a small DUB subfamily that only four members have been identified so far, including ataxin-3 (ATXN3), ataxin-3 like (ATXN3L), JOSD1, and JOSD2 [18]. As the most typical and widely investigated member, ATXN3 harbors many structural features found in Josephins compared to other DUBs. ATXN3 contains a Josephin domain at its N-terminus, followed by the catalytic site, the tandem ubiquitin (Ub)-interacting motifs (UIMs) and a polyglutamine stretch. During the catalytic processes, both UIMs and Josephin domain interact with the ubiquitin chain, where UIMs bind to proximal ubiquitins and Josephine domain connects the distal ones. Consequently, the ubiquitin chain is cleaved at the catalytic site separating ubiquitin from the substrates [396].

Josephin DUBs play pleiotropic roles in regulating multiple cellular processes, such as autophagy [397], genome integrity [398] and metabolic homeostasis [399], and its dysregulation causes several disorders. For example, mutation of ATXN3 leads to extended length of polyglutamine stretch, which aggregate or reduce the deubiquitylation-

**Table 9**
Major context-dependent OTUs.

| OTUs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Major pathological evidence (cancer relevant human specimens) | Major biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| OTUB1 | NA | **Overexpressed** in lung cancer [59], colorectal cancer [304], glioma [302], prostate cancer [684], liver cancer [303], gastric cancer [685], esophageal cancer [306], ovarian cancer [686] | **Oncogenic: Unspecified:** c-IAP1 [305]; SLC7A11 [308] **Breast cancer:** FOXM1 [300]; **Esophageal cancer:** Snail [306]; **Tumor-suppressive: Unspecified:** RPA1 [309]; **Cervical cancer:** DEPTOR [310]; **Endometrial cancer:** ERα [311] | Less potential |
| OTUD3 | **Oncogenic:** Systemic *Otud3*$^{-/-}$ inhibits initiation and progression of Kras-driven lung cancer, while systemic *Otud3* (transgenic) contributes to more susceptibility of Kras-driven lung tumorigenesis [314] **Tumor-suppressive:** Systemic *Otud3*$^{-/-}$ increases susceptibility to PyMT-driven breast cancer [314], while systemic *Otud3* (transgenic) results in less susceptibility of breast tumorigenesis [313] | **Overexpressed** in lung cancer [314] **Downregulated** in breast cancer [313], hepatocellular cancer, colon cancer, cervical cancer [314] | **Oncogenic: Lung cancer:** GRP78 [314] **Tumor-suppressive: Breast caner, hepatocellular cancer, colon cancer, cervical cancer:** PTEN [313]; **Unspecified:** TOP2A [315]; | Potential |
| A20 | **Tumor-suppressive:** Conditional *A20*$^{-/-}$ induces development of colorectal cancer among aged mice [316]; Conditional *A20*$^{-/-}$ increases susceptibility to chemically or high fat-diet-induced hepatocellular carcinoma development [317] | **Overexpressed** in breast cancer [62], esophageal cancer [318], cholangiocarcinoma [687], leukemia [319,320], skin squamous cell cancer [688], glioma [321]; **Downregulated** in liver cancer [689], nasopharyngeal cancer [322], sarcoma [327], pancreatic cancer [690], lymphoma [332,333] | **Oncogenic: Endometrial cancer:** ERα [323] | Potential |
| OTUD7B | **Oncogenic:** Systemic *Otud7b*$^{-/-}$ inhibits initiation and progression of Kras-driven lung cancer [335] | **Overexpressed** in breast cancer [336]; **Downregulated** in liver cancer [337], glioma [338] | **Oncogenic: Unspecified:** Aurora A [339], Cyclin B [339]; **Breast cancer:** EGFR [336]; **Lung cancer:** GβL [335]; **Neuroblastoma:** Sox2 [340], TRAF3 [683] | Potential |
| TRABID | NA | **Overexpressed** in breast cancer [275]; **Downregulated** in liver cancer [275] | **Oncogenic: Breast cancer:** EZH2 [275] **Tumor-suppressive: Liver cancer:** Twist1 [275] | Potential |

Note: Based on different credibility of biological evidence, if the context-dependent role of one OTU is confirmed by genetically-modified mouse models (must containing both oncogenic and tumor-suppressive models), then the evidence grade is strong. Potential grade is designated to those having both oncogenic and tumor-suppressive pathological evidence or one genetically-modified evidence plus one pathological evidence. Otherwise, the grade is designated as less potential under the remaining circumstances.

**Table 10**
Major phenotypes of UCHs knockout and transgenic mice.

| Gene | Mode | Phenotypic alterations | |
|---|---|---|---|
| | | Cancer-relevant | Cancer-irrelevant |
| *Uchl1*$^{-/-}$ | Systemic | **Lymphoma:** Resistant to Myc-induced lymphomas [387] | **Nervous:** Significantly shortened lifespan with progressive neurodegeneration in the peripheral neuromuscular system [345] and enteric nervous system [691]<br>**Endocrinal:** Significant decreases in the numbers of gonadotropes and mammotropes [692]<br>**Digestive:** Restricted proliferative ability of hepatic stellate cells induced by mitogen [693]<br>**Renal:** Glomerular hyperfiltration associated with renal neuronal dysfunction [352]; Hyperphosphatemia accompanied by phosphaturia [353]; Proteinuria, urine retention and hypotension [347]<br>**Reproductive:** Progressively decreasing spermatogonial stem cell proliferation [355] |
| | Conditional (ovum) | NA | **Reproductive:** Significantly increased rate of polyspermy and reduced litter size [356] |
| *Uchl1* (transgenic) | Systemic | **Lymphoma:** Susceptible to spontaneous development of lymphoma and lung cancer [388] | NA |
| | Conditional (testis) | NA | **Reproductive:** Sterile due to arrested spermatogenesis [348] |
| *Uchl3*$^{-/-}$ | Systemic | NA | **Nervous:** Significant learning deficit due to erroneous working memory [350]; Early-stage retinal degeneration [351]<br>**Endocrinal:** Resistant to diet-induced obesity [694] and less visceral white adipose tissue [695] |
| *Bap1*$^{-/-}$ | Systemic | **Hematological:** Malignant myeloid transformation among adult mice [344] | **Embryogenic:** Embryonic lethality [344]<br>**Immune:** Severe thymic atrophy [696] among adult mice<br>**Renal:** More sensitive to tunicamycin-induced renal damage among adult mice [375] |
| | Conditional (liver) | NA | **Digestive:** Perinatal lethality with severe hypoglycemia and hepatic lipid deficiency [346] |
| | Conditional (kidney) | NA | **Renal:** Neonatal lethality with kidney dysfunction [354] |
| | Conditional (hematopoietic cell) | **Hematological:** Malignant myeloid transformation among adult mice [344] | **Hematopoietic:** Splenomegaly, leukocytosis, anemia and progenitor expansion [357] |

related stabilization of pro-autophagy substrates in neurons [397], leading to accumulation of toxic proteins and the pathogenesis of Machado-Joseph disease (MJD). Although knockout mouse models have not been tested to verify the function of ATXN3, several comparable mouse models have been reported, displaying compelling evidence. Specifically, mice expressing ATXN3 mutant phenocopy the symptoms of MJD with significant cerebellar dystrophy and severe ataxia [400]. On the other hand, silencing mutant ATXN3 rescues motor deficits and neuropathological features in MJD mouse models [401]. Meanwhile, the neoplastic roles of Josephins have also been hinted in several reports, which are further discussed in the following chapters.

### *2.4.2. Neoplastic role of Josephins-evidence from clinical specimens and biochemical interactions*

Unlike other subfamilies of DUBs, there is limited evidence regarding the biological impacts of Josephins in cancer development, let alone genetically modified mouse models. ATXN3 seems to play a context-dependent neoplastic role since overexpression and down-regulation of ATXN3 has been identified in testicular [402] and gastric [403] cancer, respectively (Table 14). Meanwhile, ATXN3 appears to deubiquitylate and stabilize p53 to enhance cell apoptosis [404] (Tables 13 and 14). Additionally, despite lacking mechanistic explanation, ATXN3 restricts PTEN transcription in lung cancer cells to promote lung tumorigenesis [405]. Up to now, no upstream regulatory mechanism of ATXN3 in cancer has been reported.

In terms of ATXN3L, one study has found that it could deubiquitylate and stabilize KLF5 to potentially induce breast cancer proliferation [406] (Tables 13 and 14). Therefore, it appears that ATXN3L might be a potential oncogenic Josephin despite limited evidence to date. Currently, there is no consistent evidence regarding the neoplastic role of

**Table 11**
Major cancer-relevant substrates of UCHs.

| UCHs | Substrates | Modifications | Major neoplastic consequences |
|---|---|---|---|
| UCHL1 | HIF-1α | Stabilization | Promoting distant metastasis of cancer cells [395] |
| | NOXA | Stabilization | Enhanced chemo-sensitivity among cancer cells [393] |
| | p53 | Stabilization | Suppression of nasopharyngeal carcinogenesis [392] |
| UCHL3 | TDP1 | Stabilization | Enhanced topoisomerase therapy-resistance in rhabdomyosarcoma cells [364] |
| UCHL5 | TGFBR1 | Stabilization | Possible role in triggering oncogenesis [361] |
| | PRP19 | Stabilization | Promotes cell migration and invasion of liver cancer [359] |
| | Tcf7 | Altered activity | Activating oncogenic Wnt pathway in liver cancer cells [362] |
| BAP1 | H2A | Altered activity | Tumor inhibitory effects [374] |
| | Ino80 | Stabilization | Maintaining normal DNA synthesis and inhibiting tumorigenic events [370] |
| | IP3R3 | Stabilization | Inducing cell apoptosis during carcinogenic events [373] |
| | γ-tubulin | Altered activity | Preventing chromosomal instability and breast carcinogenesis [371] |
| | MCRS1 | Stabilization | Suppressing tumorigenesis of kidney cancer due to enhanced genomic stability [372] |

Note: Substrates should directly interact with and then be deubiquitylated by its corresponding DUBs based on the catalytic enzymatic functions. Those feature non-catalytical interactions or deubiquitylation by DUBs should not be considered as substrates.

**Table 12**
Major oncogenic, tumor-suppressive and context-dependent UCHs.

| UCHs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Major pathological evidence (cancer relevant human specimens) | Major biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| **Oncogenic** | | | | |
| UCHL3 | NA | **Overexpressed** in breast cancer [363] | **Rhabdomyosarcoma:** TDP1 [364] | Potential |
| UCHL5 | NA | **Overexpressed** in ovarian cancer [358], multiple myeloma [141], liver cancer [359], esophageal cancer [360] | **Unspecified:** TGFBR1 [361]; **Liver cancer:** PRP19 [359], Tcf7 [362] | Potential |
| **Tumor-suppressive** | | | | |
| BAP1 | Systemic *Bap1*$^{-/-}$ induces malignant myeloid transformation among adult mice [344]; Conditional *Bap1*$^{-/-}$ induces malignant myeloid transformation among adult mice [344] | **Downregulated** in kidney cancer [368], gallbladder cancer [697], intrahepatic cholangiocarcinoma [698], melanoma [366], osteosarcoma [699], malignant mesothelioma [367], lung cancer [377], gastric cancer [369], colorectal cancer [700] | **Unspecified:** H2A [374], Ino80 [370], IP3R3 [373]; **Breast cancer:** γ-tubulin [371]; **Kidney cancer:** MCRS1 [372] | Strong |
| **Context-dependent** | | | | |
| UCHL1 | **Oncogenic:** Systemic *Uchl1*$^{-/-}$ results in resistance to Myc-induced lymphomas [387]; Systemic *Uchl1* (transgenic) leads to higher susceptibility to spontaneous development of lymphoma and lung cancer [388] | **Overexpressed** in breast cancer [389], osteosarcoma [391], lung cancer [390]; **Downregulated** in colorectal cancer [393], melanoma [393], prostate cancer [701], nasopharyngeal cancer [392], kidney cancer [394], liver cancer [702], ovarian cancer [703] | **Oncogenic: Unspecified:** HIF-1α [395]; **Tumor-suppressive: Unspecified:** NOXA [393]; **Nasopharyngeal cancer:** p53 [392] | Potential |

Note: Based on different credibility of biological evidence, if the oncogenic or tumor-suppressive role of one UCH is confirmed by genetically-modified mouse models, then the evidence grade is strong. Otherwise, the grades are designated as potential and less potential in terms of pathological and biochemical evidence respectively. If the context-dependent role of one UCH is confirmed by genetically-modified mouse models (containing both oncogenic and tumor-suppressive models), then the evidence grade is strong. Potential grade is designated to those having both oncogenic and tumor-suppressive pathological evidence or one genetically-modified evidence plus one pathological evidence. The grade is designated as less potential under the remaining circumstances.

JOSD1 and JOSD2, which warrants further studies in the future.

### 2.5. JAMMs

#### 2.5.1. Introduction of JAMMs

Unlike other DUBs that are structurally categorized as thiol proteases, JAMMs subfamily consists of $Zn^{2+}$-dependent metalloproteases [18]. There are seven members of JAMMs identified in the human genome, namely POH1, CSN5, AMSH, AMSH-LP, BRCC36, MYSM1 and MPND. All but MPND have shown substantial catalytic activity [407,408]. Briefly, the catalytic site of JAMMs is located in the specific JAMM domain coordinating two zinc ions, which activates a water molecule to attack the isopeptide bond releasing ubiquitin chains from the attached substrates [18]. Currently, JAMMs have been shown to mediate multiple basic cellular processes, including endosomal transportation [409], proteasomal degradation [410] and DNA damage response [411], thus maintaining protein homeostasis and genomic integrity. On the other hand, dysfunctional JAMMs have also been implicated in several human pathological conditions, such as psoriasis [412], preeclampsia [413] and neoplastic events, which are further discussed in subsequent chapters.

#### 2.5.2. Physiological role of JAMMs-evidence from knockout and transgenic mouse models

JAMMs have been linked to various physiological processes based on genetically modified mouse models, including hematopoiesis and immune regulations (Table 15). Both CSN5 and MYSM1 have shown great impacts towards hematopoietic events. Systemic transgenic expression of *CSN5* increases proliferation and enhances stem cell potential of hematopoietic cells [414]. Meanwhile, global [415] or conditional [416] ablation of *Mysm1* impairs both erythropoiesis and lymphopoiesis, which is due to quiescence and increased apoptosis of hematopoietic stem cells, leading to stem cell exhaustion and defective lineage reconstitution [417]. These results suggest that both CSN5 and MYSM1 are indispensable for survival of hematopoietic stem cells and normal hematopoiesis.

So far, three JAMMs members have demonstrated potential roles in regulating the immune system. POH1 seems to negatively control immune activities, since global [418] or conditional [419] deletion of POH1 enhances the innate immune response and the onset of autoimmune disorders. Global knockout of either *Csn5* [420] or *Mysm1* [421] induces defective maturity of B cells and germinal center formation, hinting that both JAMMs are crucial for B cell development. Moreover, global deletion of *Mysm1* also leads to impaired T-cell [422] and NK cell development [423]. As for the immune response, *Mysm1*-null mice display enhanced innate and adaptive immunity, which could possibly lead to septic shock [424,425]. These results implicate a role of MYSM1 in maintaining normal immune cell development and proper immune responses.

JAMMs also regulate embryogenesis [426], osteogenesis [427] and a variety of other systems (Table 15), which imply that JAMMs might be potential therapeutic targets against relevant pathological disorders.

#### 2.5.3. Neoplastic role of JAMMs-Evidence from knockout and transgenic mouse models, clinical samples, and biochemical interactions

##### 2.5.3.1. Oncogenic JAMMs

*2.5.3.1.1. CSN5.* With the exception of AMSH-LP, all other JAMMs display potential oncogenic effects in tumorigenesis (Table 17). So far, CSN5 is the most extensively studied member of JAMMs as an oncoprotein. Despite a lack of genetically-modified mouse models, overexpression of CSN5 has been consistently detected in a variety of malignancies, such as liver cancer [428], colorectal cancer [429], lung cancer [430] and leukemia [431], where it serves as an unfavorable prognostic factor (Table 17). Currently, several major substrates have been verified to mediate the oncogenic effects of CSN5, including PD-L1 [432], Trx [431], Snail [433], survivin [434], FOXM1 [435] and ZEB1

**Table 13**
Major cancer-relevant substrates of Josephins.

| Josephins | Substrates | Modifications | Major neoplastic consequences |
|---|---|---|---|
| ATXN3 | p53 | Stabilization | Potential role in inducing cancer cell apoptosis [404] |
| ATXN3L | KLF5 | Stabilization | Promoting breast cancer proliferation [406] |

Note: Substrates should directly interact with and then be deubiquitylated by its corresponding DUBs based on the catalytic enzymatic functions. Those feature non-catalytical interactions or deubiquitylation by DUBs should not be considered as substrates.

[436] (Tables 16 and 17). Specifically, the deubiquitylation and stabilization of PD-L1 by CSN5 confer resistance to anti-CTLA4 therapy [432]. Moreover, through stabilization of Snail [433], FOXM1 [435] and ZEB1 [436], CSN5 upregulate metastasis-related transcriptome to enhance the invasion and migration of lung, pancreatic and kidney cancers. Via stabilizing Trx [431] and survivin [434] that links oxidative-stress and anti-apoptotic responses, CSN5 markedly boosts the growth of leukemic and lung cancer cells. Besides its deubiquitylation enzymatic activity, CSN5 also induces cytoplasmic transport and proteasomal degradation of tumor suppressive proteins, such as p27 [437], to mitigate pathogenesis of ovarian [438], nasopharyngeal [439] and pancreatic [439] cancer.

The upstream regulatory mechanisms of CSN5 in tumorigenesis have also been comprehensively studied. Expression of CSN5 is activated at the transcriptional level by STAT3 [440], C/EBP-beta2 [441] and HER-2/neu [442] to enhance the malignant progression of diverse cancers. Regarding post-transcriptional modifications, CSN5 was targeted by several miRNAs, including let-7d in breast cancer [443] and miR-24-3p in nasopharyngeal cancer [444], to suppress tumorigenesis. Meanwhile, several proteins could also directly interact and compete with CSN5 for binding its substrate proteins. For instance, both C10ORF97 [445] and VDUP1 [446] function as tumor suppressors via interacting with CSN5, thereby reducing the cytoplasmic transport of p27, and culminates in nuclear sequestration of p27 and transcription of tumor suppressive targets. Moreover, the interaction between MIF and CSN5 could also result in the inhibitory effects on AP-1 transcriptional activation and end up with the upregulation of p27 expression level [447]. Taken together, we believe that CSN5 is a potential oncogenic JAMM member despite lacking genetically modified mouse model evidence (Fig. 4).

Several pathological reports have confirmed the upregulation of POH1 in a variety of cancers, such as liver cancer [448], colorectal cancer [449] and multiple myeloma [450] (Table 17), which correlates with poor prognosis among cancer patients. Also, both BRCC36 and MYSM1 are overexpressd in several cancer types including cervical [451], glioma [452], melanoma [453] and colorectal [454] cancers (Table 17). However, a better understanding of the upstream and downstream regulatory mechanisms of these JAMMs is necessary to dissect their roles in the biology of human cancers.

## 3. Clinical implications of DUB inhibitors

### 3.1. Major inhibitors that target USPs as anti-cancer agents

In light of the oncogenic role of USPs in a variety of cancers, selective inhibitors have been discovered or synthesized to specifically target the USPs and attenuate their oncogenic functions, especially those against USP1, USP7 and USP14 (Table 18).

USP1 is an extensively investigated USP that displays oncogenic functions in various malignancies. So far, three highly specific inhibitors of USP1 have been identified, namely ML323 [455], SJB2–043 [456] and SJB3-019A [457] (Table 18). ML323 selectively and reversibly inhibits the enzymatic activity of USP1 at nanomolar concentrations, through an allosteric mechanism that alters the structure of the ubiquitin-binding motif in USP1 [455]. Without substantial cytotoxicity to normal cells, ML323 potentiates cisplatin sensitivity in non-small cell lung cancer and osteosarcoma cells, which is mechanistically attributes to DNA damage response in cancer cells, implying that ML323 may overcome resistance of platinum-based anti-tumor drugs [455]. SJB2–043, a chemically-synthesized small-molecule inhibitor that disrupts the formation of Ub-USP1 conjugate to inhibit the enzymatic activity of USP1, leading to proliferation in leukemic cells [456]. SJB3-019A is an irreversible, concentration-dependent, specific inhibitor of USP1. SJB3-019A suppresses USP1-mediated disassembly of the ubiquitin chains, thereby reducing the ability of DNA repair to induce apoptosis of multiple myeloma cells [457]. On the other hand, there are also two non-selective USP1 inhibitors have been reported, including GW7647 and pimozide [458]. Both these molecules are allosteric inhibitors, binding to sites other than the active center of USP1 to exert their inhibitory effect. Functionally, both inhibitors demonstrate anti-tumor effects in lung cancer cells, which might also be linked to the damaged DNA repair responses [458]. As non-selective inhibitors, both GW7647 and pimozide could also structurally inhibit the enzymatic activity of USP7, although no functional impact has been reported so far [458] (Table 18). Unfortunately, none of these USP1 inhibitors have been tested in clinical trials for their anti-cancer efficacies.

Several effective inhibitors against USP7 have been developed, with most of which displaying high specificity (Table 18). Compound 4 is a noncompetitive USP7 inhibitor with unknown structural mechanism.

**Table 14**
Major oncogenic and context-dependent Josephins.

| Josephins | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Major pathological evidence (cancer relevant human specimens) | Major biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| **Oncogenic** | | | | |
| ATXN3L | NA | NA | **Breast cancer:** KLF5 [406] | Less potential |
| **Context-dependent** | | | | |
| ATXN3 | NA | **Overexpressed** in testicular cancer [402]; **Downregulated** in gastric cancer [403] | **Tumor-suppressive: Unspecified:** p53 [404] | Potential |

Note: Based on different credibility of biological evidence, if the oncogenic role of one Josephin is confirmed by genetically-modified mouse models, then the evidence grade is strong. Otherwise, the grades are designated as potential and less potential in terms of pathological and biochemical evidence respectively. If the context-dependent role of one Josephin is confirmed by genetically-modified mouse models (containing both oncogenic and tumor-suppressive models), then the evidence grade is strong. Potential grade is designated to those having both oncogenic and tumor-suppressive pathological evidence or one genetically-modified evidence plus one pathological evidence. The grade is designated as less potential under the remaining circumstances.

**Table 15**
Major phenotypes of JAMMs knockout and transgenic mice.

| Gene | Mode | Phenotypic alterations | |
|---|---|---|---|
| | | Cancer-relevant | Cancer-irrelevant |
| *Poh1*$^{-/-}$ | Conditional (myeloid cell) | NA | **Immune:** Aggravated LPS-induced systemic inflammation and alum-induced peritonitis inflammatory responses [418] |
| | Conditional (T-cell) | NA | **Immune:** Disrupted immune tolerance and early onset of fetal autoimmune disorders due to impaired development and differentiation of Treg cells [419] |
| *Csn5*$^{-/-}$ | Systemic | NA | **Embryogenic:** Early embryonic lethality [426] |
| | Conditional (B cell) | NA | **Immune:** Impaired B cell development and germinal center formation [420] |
| | Conditional (chondrocyte) | NA | **Osteogenic:** Neonatal lethal chondrodysplasia with severe dwarfism [427] |
| | Conditional (kidney) | NA | **Renal:** Familial hyperkalemic hypertension-like phenotypes [704] |
| | Conditional (liver) | NA | **Digestive:** Liver degeneration with defective regenerative ability and shorted survival of hepatocytes [705] |
| | Conditional (myeloid cell) | NA | **Cardiovascular:** Significantly exacerbated formation of atherosclerotic lesion [706] |
| | Conditional (osteochondral progenitor cell) | NA | **Osteogenic:** Drastically shortened limbs at birth [707] |
| | Conditional (Schwann cell) | NA | **Nervous:** Motor dysfunction due to dysmyelinating neuropathy [708] |
| *Csn5* (transgenic) | Systemic | NA | **Hematopoietic:** Development of myeloproliferative disorder with extended survival, increased proliferation and enhanced potential of hematopoietic cells [414] |
| *Amsh*$^{-/-}$ | Systemic | NA | **Nervous:** Early postnatal lethality with severe growth retardation and neurodegeneration [709] |
| *Mysm1*$^{-/-}$ | Systemic | NA | **Hematopoietic:** Impaired hematopoiesis with lymphopenia, anemia and thrombocytosis, as well as defective lymphocyte differentiation [415]; Impaired quiescence and increased apoptotic rate of hematopoietic stem cells, leading to exhaustion of stem cell pool and defective self-renewal and lineage reconstituting abilities [417]<br>**Immune:** Impaired B cell development [421]; Defective T-cell development and reduced thymocyte survival [422]; Increased resistance to experimental cerebral malaria with less amount, hyper-activation and higher cytokine production of cytotoxic T-cells [710]; Impaired maturation of NK cells [423]; Unrestrained MDP-induced peritonitis, systemic inflammation and liver injury [424]; Hyper-inflammation and enhanced viral clearance but also susceptibility to septic shock due to overzealous self-destructive immune response [425]<br>**Osteogenic:** Osteopenia and skeletal anomalies, including a truncated tail and shorter hind limbs [711]; Lower bone mass with enhanced autonomous differentiation and accelerated adipogenesis of mesenchymal stem cells [712]<br>**Dermal:** Skin atrophy and reduced skin cellularity [713]; "Belly-spot-and-tail" phenotype featuring pigmentation defect and altered melanocyte specification [453] |
| | Conditional (bone marrow) | NA | **Hematopoietic:** Defective hematopoiesis due to impaired hematopoietic stem cell quiescence and survival [416] |
| | Conditional (B cell) | NA | **Immune:** Impaired B cell differentiation, survival and proliferation [714] |

Functionally, through destabilizing Mdm2 to increase in p53 levels, Compound 4 exerts its tumor-suppressive effects in leukemia and prostate cancer cells [459]. Both FT671 and FT827 are ubiquitin-competitive small molecule inhibitors. FT671 could non-covalently occupy the catalytic center while the covalent FT827 enables its vinylsulfonamide moiety to form a covalent bond with active center, therefore hindering the conjugation between ubiquitin and USP7. Both highly selective inhibitors exhibit potent anti-tumor activity against multiple myeloma, which is also attributed to the destabilization on Mdm2 [460]. GNE-6640 and GNE-6776 are two orally-active specific inhibitors of USP7, which bind to the catalytic triad located at the interface of the USP7 catalytic domain, sterically inhibiting the formation of ubiquitin-USP7 conjugation and preventing transition of the USP7 catalytic domain into an active conformation. Similarly, these two drugs strongly inhibit the enzymatic activity of USP7, leading to proteasomal degradation of Mdm2 and great anti-tumor efficacy in preclinical leukemia models [461]. P5091 is a dose-dependent ubiquitin-competitive USP7 inhibitor, which specifically inhibits the conjugate formed between ubiquitin and USP7 catalytic domain [122]. Currently, numerous data has demonstrated that inhibition of USP7 by P5091 leads to tumor suppression in a variety of preclinical cancer models, such as multiple myeloma [122], lung cancer [462] and melanoma [463], by blocking USP7/Mdm2 interaction. Apart from highly selective inhibitors, four non-selective USP7 inhibitors have also been developed, including Compound 1 [464], HBX 41108 [465], P22077 [466] and Ursolic acid [467] (Table 18). For example, P22077 is an

**Table 16**
Major cancer-relevant substrates of JAMMs.

| JAMMs | Substrates | Modifications | Major neoplastic consequences |
|---|---|---|---|
| POH1 | E2F1 | Stabilization | Promoting development of liver cancer [448] |
| CSN5 | PD-L1 | Stabilization | Reduced sensitivity of cancer cells to anti-CTLA4 therapy [432] |
| | Trx | Stabilization | Promoting progression of leukemia [431] |
| | Snail | Stabilization | Inducing lung cancer metastasis [433] |
| | survivin | Stabilization | Increased growth of lung cancer cells [434] |
| | FOXM1 | Stabilization | Enhancing invasion and metastasis of pancreatic cancer [435] |
| | ZEB1 | Stabilization | Promoting metastasis of renal cell cancer [436] |
| AMSH | Slug | Stabilization | Maintaining the metastatic potential of melanoma [715] |
| BRCC36 | NuMA | Altered activity | Possible role in triggering cancer cell division and proliferation [716] |
| MYSM1 | H2A | Altered activity | Suppression on oncogenic transcriptional activities [717] |

Note: Substrates should directly interact with and then be deubiquitylated by its corresponding DUBs based on the catalytic enzymatic functions. Those feature non-catalytical interactions or deubiquitylation by DUBs should not be considered as substrates.

**Table 17**
Major oncogenic JAMMs.

| JAMMs | Physiological evidence (cancer relevant knockout or transgenic mouse models) | Major pathological evidence (cancer relevant human specimens) | Major biochemical evidence (cancer relevant substrates) | Evidence grade |
|---|---|---|---|---|
| POH1 | NA | **Overexpressed** in liver cancer [448], esophageal cancer [449], colorectal cancer [449], multiple myeloma [450], breast cancer [718] | **Liver cancer:** E2F1 [448] | Potential |
| CSN5 | NA | **Overexpressed** in pancreatic cancer [435], breast cancer [719], lung cancer [430], colorectal cancer [429], liver cancer [428], ovarian cancer [438], kidney cancer [436], leukemia [431], glioma [720], nasopharyngeal cancer [444], thyroid cancer [721] | **Unspecified:** PD-L1 [432]; **Leukemia:** Trx [431]; **Lung cancer:** Snail [433], survivin [434]; **Pancreatic cancer:** FOXM1 [435] **Kidney cancer:** ZEB1 [436] | Potential |
| AMSH | NA | NA | **Melanoma:** Slug [715] | Less potential |
| BRCC36 | NA | **Overexpressed** in cervical cancer [451], glioma [452] | **Unspecified:** NuMA [716] | Potential |
| MYSM1 | NA | **Overexpressed** in melanoma [453], colorectal cancer [454] | **Unspecified:** H2A [717] | Potential |

Note: Based on different credibility of biological evidence, if the oncogenic role of one JAMM is confirmed by genetically-modified mouse models, then the evidence grade is strong. Otherwise, the grades are designated as potential and less potential in terms of pathological and biochemical evidence respectively.

analog of P5091 with high affinity to both USP7 and USP47 [468], which demonstrates anti-cancer activity against a variety of malignancies, including neuroblastoma [466], leukemia [469] and melanoma [463]. Taken together, these results suggest great potential of USP7 inhibitors as anti-cancer drugs, which may need further preclinical studies and clinical trials in the future.

All of the USP14 inhibitors are non-selective inhibitors, since other 19S proteasome-associated DUBs such as UCHL5 share structural similarity with USP14 (Table 18). b-AP15 is a representative member of all USP14 inhibitors. Mechanistically, the β carbons in b-AP15 serve as Michael acceptor moieties that confer covalent binding to cysteine residues in active center of both USP14 and UCHL5, which reversibly and competitively inhibits the conjugation between ubiquitin and catalytic domain [470]. The anti-tumor effects of b-AP15 have been confirmed in both solid and hematological malignancies, such as leukemia [470], multiple myeloma [141] and prostate cancer [471], which features different biochemical mechanisms compared to bortezomib, since its anti-tumor effects are not impacted by the levels of p53 or overexpression of the apoptosis inhibitor BCL2 [470]. WP1130 is another non-selective USP14 inhibitor, which also demonstrates broad affinity with USP5, USP9X, USP17 and UCHL5 [472]. Similar as other major DUB inhibitors, WP1130 also hinders the conjugate formation of Ub-USP14 in the active site to suppress lymphoid tumorigenesis [472]. Meanwhile, WP1130 have also been verified in multiple myeloma [473], breast cancer [159] and leukemia [474], implicating a potent anti-cancer efficacy in multiple cancers. VLX1570, an analog of b-AP15 with higher potency and solubility, is also a reversible non-selective competitive inhibitor of USP14 which targets the formation of Ub-USP14 or Ub-UCHL5 conjugates [475]. Via inhibiting the enzymatic activity of USP14 and UCHL5, VLX1570 display significant anti-cancer efficacy in multiple myeloma [475], Waldenstrom macroglobulinemia [142] and Ewing sarcoma [476]. Based on these findings, a phase 1/2 trial evaluating the efficacy and tolerability of VLX1570 among patients with relapsed or refractory multiple myeloma is ongoing (NCT02372240). Moreover, several metal-chelating complexes could specifically target 19S proteasome-associated DUBs (Table 18), such as USP14 and UCHL5 [477]. Functionally, copper [477], gold [478], platinum [479] or nickel chelated with pyrithione [480] display significant anti-tumor effects among both solid and hematological cancers.

Apart from inhibitors that target USP1, USP7 and USP14, other small-molecule inhibitors are also believed to have potential anti-cancer effects by inhibiting the enzymatic activity of DUBs (Table 18), such as EOAI3402143 that targets both USP9X and USP24 to suppress cancer progression in multiple myeloma [481]. However, more preclinical and clinical trials are required before its clinical applications.

### *3.2. Major inhibitors that target non-USP DUBs as anti-cancer agents*

Given that few non-USP DUBs have been linked to cancer development, the number of inhibitors that target non-USP DUBs as anti-cancer agents is also limited, with exception of UCHL5 and POH1 (Table 19).

As discussed in detail above, inhibitors that target UCHL5 could also inhibit the enzymatic activity of USP14 (Table 19). Capzimin, a derivative of the non-selective inhibitor 8-thioquinoline (8TQ), serves as a highly specific inhibitor of POH1 [407]. Similar to 8TQ [482], Capzimin could also non-competitively inhibit the activity of POH1 by directly binding to the catalytic $Zn^{2+}$ ion, leading to anti-tumor effects in both colorectal and lung cancer. Meanwhile, O-phenanthroline (OPA) is also a highly selective inhibitor of the enzymatic activity of POH1, which induces apoptosis among multiple myeloma cells and overcomes Bortezomib resistance [450]. However, relevant preclinical and clinical validation is required to test therapeutic efficacies of these compounds.

**Table 18**
Major USP inhibitors and their anti-cancer effects.

| USPs | Inhibitor | Mechanism | Major effective cancer types |
|---|---|---|---|
| USP1 | ML323 | Highly selective; Reversible | Lung cancer and osteosarcoma [455] |
| | SJB2-043 | Highly selective | Leukemia [456] |
| | SJB3-019A | Highly selective; Irreversible | Multiple myeloma [457] |
| | GW7647 | Non-selective; Reversible | Lung cancer [458] |
| | Pimozide | Non-selective; Reversible | Lung cancer [458] |
| USP2 | LCAHA | Non-selective | Colorectal cancer [722] |
| | ML364 | Non-selective; Reversible | Colorectal cancer and lymphoma [723] |
| USP5 | WP1130 | Non-selective | Multiple myeloma [473]; Lymphoma [472] |
| USP7 | Compound 4 | Highly selective | Leukemia and prostate cancer [459] |
| | FT671 | Highly selective | Multiple myeloma [460] |
| | FT827 | Highly selective | Multiple myeloma [460] |
| | GNE-6640 | Highly selective | Leukemia [461] |
| | GNE-6776 | Highly selective | Leukemia [461] |
| | P5091 | Highly selective | Multiple myeloma [122]; Lung cancer [462]; Colorectal cancer [126]; Prostate cancer [624]; Melanoma [463] |
| | Compound 1 | Non-selective | Multiple myeloma and leukemia [464] |
| | HBX 41108 | Non-selective; Reversible | Colorectal cancer [465] |
| | P22077 | Non-selective | Neuroblastoma [466]; Leukemia [469]; Melanoma [463] |
| | Ursolic acid | Non-selective | Multiple myeloma [467] |
| USP8 | MB7295 | Highly selective | Lung cancer [724] |
| USP9X | EOAI3402143 | Non-selective; Reversible | Multiple myeloma [481] |
| | WP1130 | Non-selective; Reversible | Lymphoma [472]; Multiple myeloma [481]; Breast cancer [725]; Liver cancer [726]; Leukemia [474]; Lung cancer [727]; Prostate cancer [728] |
| USP11 | Mitoxantrone | Non-selective | Pancreatic cancer [729] |
| USP14 | Auranofin | Non-selective | Leukemia [730] |
| | b-AP15 | Non-selective; Reversible | Leukemia, squamous cancer, lung cancer, breast cancer, colorectal cancer [470]; Multiple myeloma [141]; Prostate cancer [471]; Liver cancer [731] |
| | Cadmium pyrithione | Non-selective | Leukemia [732] |
| | Copper pyrithione | Non-selective | Liver cancer [477] |
| | Gold pyrithione | Non-selective | Leukemia and lung cancer [478] |
| | Nickel pyrithione | Non-selective | Leukemia [480] |
| | Platinum pyrithione | Non-selective | Breast cancer [479]; Ovarian cancer [733]; Lung cancer [734] |
| | Silver disulfiram | Non-selective | Lung cancer [735] |
| | WP1130 | Non-selective | Lymphoma [472] |
| | VLX1570 | Non-selective; Reversible | Multiple myeloma [475]; Waldenstrom macroglobulinemia [142]; Ewing sarcoma [476] |
| USP17 | WP1130 | Non-selective | Breast cancer [159] |
| USP24 | EOAI3402143 | Non-selective; Reversible | Multiple myeloma [481] |
| USP25 | AZ1/2/3/4 | Non-selective; Reversible | Colorectal cancer [736] |
| USP28 | AZ1/2/3/4 | Non-selective; Reversible | Colorectal cancer [736] |
| USP47 | Compound 1 | Non-selective | Multiple myeloma and leukemia [464] |

Note: Inhibitors should inhibit the deubiquitylation activity rather than any other modifications such as deneddylation. “Highly selective”: Those inhibitors target only one USP member; “Non-selective”: Those inhibitors target more than one USP member.

## 4. Summary and future perspective

Owing to accumulating scientific discoveries in the past decades, DUBs have been found to be extensively involved in various physiological and pathological processes. Through deubiquitylation of downstream substrates, DUBs could antagonize the biological effects of E3 ubiquitin ligases to exert oncogenic or tumor suppressive functions. Meanwhile, as proteases, the expression level and enzymatic activity of DUBs could also be regulated via various mechanisms, such as transcriptional, post-transcriptional, and post-translational modifications,

**Table 19**
Major inhibitors that target non-USP DUBs as anti-cancer agents.

| DUBs | Inhibitor | Mechanism | Major effective cancer types |
|---|---|---|---|
| TRABID | NSC112200 | Highly selective | Breast Cancer [66] |
| UCHL5 | Auranofin | Non-selective | Leukemia [730] |
| | b-AP15 | Non-selective; Reversible | Leukemia, squamous cancer, lung cancer, breast cancer, colorectal cancer [470]; Multiple myeloma [141]; Prostate cancer [471]; Liver cancer [731] |
| | Cadmium pyrithione | Non-selective | Leukemia [732] |
| | Copper pyrithione | Non-selective | Liver cancer [477] |
| | Gold pyrithione | Non-selective | Leukemia and lung cancer [478] |
| | Nickel pyrithione | Non-selective | Leukemia [480] |
| | Platinum pyrithione | Non-selective | Breast cancer [479]; Ovarian cancer [733]; Lung cancer [734] |
| | Silver disulfiram | Non-selective | Lung cancer [735] |
| | WP1130 | Non-selective | Lymphoma [472] |
| | VLX1570 | Non-selective; Reversible | Multiple myeloma [475]; Waldenstrom macroglobulinemia [142]; Ewing sarcoma [476] |
| POH1 | Capzimin | Highly selective | Colorectal cancer [407] |
| | 8-thioquinoline | Non-selective | Lung cancer [482] |
| | O-phenanthroline | Highly selective | Multiple myeloma [450] |

Note: Inhibitors should inhibit the deubiquitylation activity rather than any other modifications such as deneddylation. “Highly selective”: Those inhibitors target only one DUB member; “Non-selective”: Those inhibitors target more than one DUB member.

to engage in cancer development. Therefore, DUBs play an important role in cancer signaling networks, to impact on disease progression. Moreover, by targeting the oncogenic DUBs, multiple potent inhibitors suppressing their enzymatic activity are currently being developed with potent anti-cancer efficacy in preclinical models. Nevertheless, it should also be noted that more selective inhibitors that do not target the highly conserved active sites (His and Cys domains) of DUB are needed to improve drug efficacy while reducing non-specific toxicity. Hence, more in-depth mechanistic studies as well as preclinical and clinical trial results are needed to facilitate the clinical use of DUB inhibitors as anti-cancer agent.

There are also interesting research directions that are worthy of further in-depth investigation. For example, in terms of the regulation of DUB expression levels, increased CpG island methylation correlates with higher *USP44* transcription among pluripotent stem cells [483]. REST-associated G9a-dependent histone methylation is found to repress the transcription of *USP37*, which contributes to the development of medulloblastoma [484]. These findings suggest that epigenetic status may regulate the expression level of DUBs under specific circumstances, in addition to traditional regulatory mechanisms that we discussed above. Therefore, clarifying the epigenetic regulations of DUBs will advance our understanding of DUB biology in cancer. In addition, cancer metabolism has also become an important research focus in recent years. To this end, it has been reported that BAP1 is able to deubiquitylate H2A and thus lead to transcriptional suppression on SLC7A11, which ultimately causes cellular ferroptosis and tumor suppression [376,485]. Therefore, a greater understanding between DUBs activity and cancer-relevant metabolic alterations may be a fruitful area of study in the future. Furthermore, a recent research study by Bouchard and colleagues has demonstrated that cancer mutations could damage the formation of substrate-driven phase separation of SPOP, which results in the tumor progression in multiple malignancies [486]. Due to the close functional interactions and reciprocity between DUBs and E3 ligases, whether phase separation is also involved in the regulation of DUBs and whether substrates could likewise drive phase separation of certain cancer-associated DUBs are worth studying in the future. Taken together, research advances of DUBs over the past decades has revealed their critical roles in the development of a wide variety of human cancers, and highlighted the promising future of DUB inhibitors as anti-cancer drugs.

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