Roles of ubiquitin-specific protease 13 in normal physiology and tumors (Review)

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Abstract. Ubiquitin-specific protease 13 (USP13) is one of the most important deubiquitinases involved in various diseases. As deubiquitinases are components of the deubiquitination process, a significant post-translational modification, they are potential treatment targets for different diseases. With recent technological developments, the structure of USP13 and its pathological and physiological functions have been investigated. However, USP13 expression and function differ in various diseases, especially in tumors, and the associated mechanisms are complex and remain to be fully investigated. The present review summarized the recent discoveries and the current understanding of the USP13 function in tumors.

Contents

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1. Introduction

Ubiquitination is the reversible modification process of the binding of an ubiquitin protein or ubiquitin chain to target proteins; ubiquitin-proteasome ultimately degrades target proteins (1). Ubiquitination is one of the most important post-translational modifications that regulate the structure, location, activity and degradation of substrates (1), and is associated with several cellular processes, such as protein degradation, DNA damage repair, cell cycle, signal transduction, cell division and immune reactions (2,3).

Ubiquitination involves E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes and E3 ubiquitin ligases (4). To catalyze the process of ubiquitination, ubiquitin forms a covalent linkage through its glycine with the lysine residues of the substrate protein (1). Ubiquitin also binds with other molecules, such as the N-terminal residue of p21, serine and threonine of the major histocompatibility complex-I heavy chain and phospholipids, leading to the degradation of these proteins (5-7). K48- and K63-linked polyubiquitin chains are the main polyubiquitin chains. The K48-linked ubiquitin chains mainly function in the ubiquitin-proteasome degradation of target proteins, while the K63-linked polyubiquitin chains mainly function in lysosomal degradation and regulation of DNA repair and immune response by increasing the recruitment of repair factors through the interactions between K63-linked polyubiquitin chains and the Ile44 patch in ubiquitin and acting as docking sites for signaling molecules in the immune response (8,9). By contrast, deubiquitination refers to the removal of ubiquitin from a target protein by deubiquitinases (DUBs) (10). DUBs regulate the process of deubiquitination in several ways, such as handling the ubiquitin precursor, shearing the ubiquitin chain and removing ubiquitin chains from the target protein. DUBs not only directly deubiquitinate target proteins, but also regulate E3 ubiquitin ligases. For instance, ubiquitin-specific protease 13 (USP13) stabilizes the expression of the ubiquitin ligase Siah2 via binding to Siah2 through its ubiquitin-associated (UBA) domains (11). To date, ≥100 DUBs have been identified, which are divided into two major families, the cysteine proteases and the metalloproteases (4,12). DUBs can be further divided into seven families according to their structure, namely ubiquitin C-terminal hydrolase, ubiquitin-specific protease, ovarian

tumor proteases, Machado-Josephin domain superfamily, motif interacting with ubiquitin-containing novel DUB family, zinc finger with UFM1-specific peptidase domain protease and JAB1/MPN/MOV34 metalloenzyme (13). JAMMs are metalloproteases, while the rest of the aforementioned families of DUBs are cysteine proteases.

The USP family contains various members that play an important role in the regulation of ubiquitin-proteasome and stabilize the expression of their substrates, such as USP5 and 17. USP5 is a core fitness protein in the inhibition of the accumulation of free ubiquitin chains, while USP17 is essential for the proliferation of different tumor cells such as osteosarcoma and prostate cancer cells (14). USP13, also called isopeptidase T-3, belongs to the USP family and was first identified by Timms *et al* (15) in 1998. The USP13 gene is located in the 'OncCassette' locus present at 3q26.2-3q26.3 (13,16). The USP13 protein consists of 863 amino acids with a molecular mass of 97,327 Da, and is widely expressed in various types of cells such as immune cells. As a protein enriched in immune cells, especially in T cells, USP13 plays a notable role in regulating the immune response via interactions with various proteins, such as STING, and is positively associated with the infiltration levels of type 2 T helper cells and central memory CD4^{+} T cells in prostate cancer (17). USP13 has a complicated role in cell proliferation and apoptosis by regulating cell circle, autophagy and signal transduction in both normal and tumor cells (18,19). It is also closely associated with several diseases such as inflammation and tumors, in which it regulates cell functions through ubiquitin-proteasome-dependent or -independent pathways (20). USP13 plays a marked regulatory role in the occurrence and development of diseases, and research is on the increase. In the present review, the focus was on recent advances in understanding the physiological functions of USP13 and its role in tumor development. As an important enzyme in post-translational modification, USP13 is a potential therapeutic target.

2. Domain architectures of USP13

USP13 contains a USP domain and a ZnF ubiquitin binding domain. Cys- and His-box are lobes of the catalytic domain. The USP domain contains two UBA domains (Fig. 1). The zinc core in the ZnF domain coordinates with the peptide chain in a C3H pattern. Overall, the solution structure of USP13 contains a β-sheet of five strands flanked by two α-helices, forming an α/β sandwich fold (21). USP13 cannot hydrolyze free polyubiquitin chains; however, it stabilizes the expression of specific substrates such as phosphatase and tensin homolog (PTEN) (21). K48-linked ubiquitin chains mainly function in ubiquitin-proteasome degradation by providing signals for proteolysis by the 26S proteasome, whereas the K63-linked ubiquitin chains are closely associated with DNA repair, endocytosis, immune response and lysosomal degradation (2,22). K63-linked ubiquitin chains are involved in lysosomal degradation via engagement with the Endosomal Sorting Complex Required for Transport (ESCRT) machinery. Components of the ESCRT pathway prevent the binding of K63-ubiquitinated proteins to the 26S proteasome subunit, thus targeting them to the lysosomal pathway. USP13 mainly catalyzes the hydrolysis of K63-linked ubiquitin chains attached to target

proteins, thereby regulating cell function. The UBA domain of USP13 promotes substrate and enzyme binding, while the ZnF domain facilitates enzyme hydrolysis (8). The tandem UBA domain interacts with ubiquitin and acts as the receptor for its catalytic activity (2). At present, proteomics approaches with high sensitivity and accuracy such as two-dimensional fluorescence difference gel electrophoresis (2D-DIGE) have been applied to identify novel substrates of proteins and to investigate their function. For instance, vinculin was identified as a substrate of USP13 using 2D-DIGE in 293T cells. This finding suggests that, as one of the major constituents contributing to intercellular communication, the expression of vinculin may be regulated by deubiquitination (21). Owing to the complexity of the structure, the functions of the different domains of USP13 warrant further investigations.

3. USP13 in normal physiology

Regulation of the cell cycle
Stabilizing the mitotic kinase Aurora B. Aurora kinase, a major regulator of the cell cycle, belongs to a family composed of three serine/threonine kinases. Among them, Aurora B, a mitotic kinase, is necessary for chromosome segregation and cytokinesis. It influences mitosis and ensures correct segregation of chromosomes, and its expression is associated with genome stability (23,24). Abnormal expression of Aurora B is related to the generation and progression of cancer, and therefore can potentially be explored for the treatment of cancer (25,26).

The expression of Aurora B is regulated by ubiquitination and deubiquitination, thus affecting the cell cycle (27). USP13 and the ubiquitin recognition factor in endoplasmic reticulum (ER)-associated degradation 1, which is essential in the degradation of ubiquitylated substrates via interaction with valosin-containing protein, stabilize the expression of Skp2, an important molecular which promotes the destruction of numerous tumor suppressor proteins, thereby influencing cell cycle and ER-associated degradation (ERAD). USP13 interacts with Aurora B and stabilizes its expression, mainly in the G2-M transition of the cell cycle, thus allowing an enzymatically independent increase in Aurora B levels (28). Aurora B also phosphorylates USP13 at Ser114 to promote the interaction between them and stabilizes the expression of Aurora B (29).

Taking part in DNA replication repair. Topoisomerase IIβ-binding protein 1 (TopBP1) is a DNA replication repair protein that binds to the essential DNA replication protein Treslin and takes part in the initiation of DNA replication. The expression of TopBP1 is upregulated in the G1/S transition and is regulated by post-translational modifications such as acetylation and ubiquitination (30-32). USP13 regulates the stability of TopBP1 through the ubiquitin-proteasome pathway and stabilizes the expression of TopBP1. TopBP1 activates the ATR signaling pathway to initiate the replication checkpoint during the replication stress response (33).

Cohesin is a protein that regulates DNA replication and repair, thereby affecting the cell cycle. Cohesin is up or downregulated by its post-translational modifications, which include the extensively studied acetylation of its core subunit SMC3,
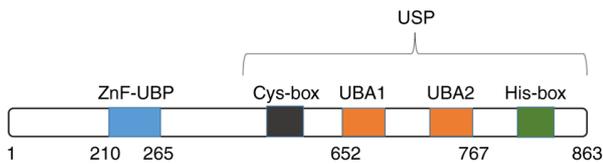
Figure 1. Domain architectures of USP13. ZnF, zinc finger; UBP, ubiquitin-specific processing protease; USP, ubiquitin-specific protease; UBA, ubiquitin associated.

and ubiquitination. USP13 and cohesin interact especially during DNA replication, and USP13 regulates the ubiquitination/deubiquitination of the interacting subunit of cohesion through its UBA1/2 domain (34).

Promoting the ERAD process. The ER is important for maintaining cell stability. ERAD is activated by protein kinase-like ER kinase, the type II transmembrane glycoprotein ATF6 and other ER-stress sensors. Dysfunction of this process is associated with numerous pathologies, including inflammation and tumor formation (35,36). USP13 participates in ERAD by interacting with gp78, an E3 ligase homologous to Hrd1p, and plays an important role in promoting ERAD. USP13 antagonizes gp78 by removing ubiquitin. The second UBA domain of USP13 is involved in this interaction. Furthermore, gp78 and USP13 form a complex with the nucleocytoplasmic shuttling protein Bcl-2-associated athanogen-6 (Bag6) to promote its interaction with small glutamine-rich tetratricopeptide repeat-containing protein α, modulating the ERAD process (37). USP13 also downregulates the ubiquitination of Bag6 cofactor ubiquitin-like protein 4A via gp78 to downregulate Bag6 clipping, a proteolytic process, thus maintaining the function of Bag6 and promoting the ERAD process (37).

Regulation of autophagy. Autophagy promotes the degradation of damaged cellular organelles, maintains the stability of the cellular environment, and is closely associated with cell functions (38,39). NEDD4, an E3 ubiquitin ligase, stabilizes phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3) through the ubiquitin-proteasome pathway. NEDD4 undergoes auto-ubiquitination at K1279 and recruits USP13 to form a deubiquitination complex that regulates the ubiquitination of PIK3C3. In this process, the K48-linked polyubiquitin chains added to K419 lead to proteasomal degradation of PIK3C3 and promote autophagy. USP13 also promotes the expression of autophagy-related proteins by interacting with the Vps34 complex (37,40,41).

4. Regulation of USP13 signaling

In general, the regulatory mechanisms involving DUBs include post-translational modifications, and substrate- and inhibitor-induced changes. DUBs play various roles by regulating the catalytic activity, number and location of their substrates (42).

Aurora B and ataxia telangiectasia mutated (ATM) regulate the expression of USP13 via phosphorylation of USP13 at Ser114 and Thr196 to promote the interaction between them, respectively, while the CDC-like kinase 3 (CLK3)-Q607R

mutation induces the phosphorylation of USP13 at Tyr708 and promotes its association with c-Myc (43). USP13 stabilizes its substrate, and at the same time, the activity of USP13 is upregulated by CLK3 via promoting phosphorylation of USP13 at Tyr708, which increases its deubiquitinating enzyme activity. In conclusion, the expression USP13 is regulated by its substrates through their interaction to regulate downstream signal transduction.

5. Role of USP13 in tumors

Dysregulation of USP13 in tumors. The expression and function of USP13 varies in different tumors. For instance, in breast cancer, high USP13 expression is associated with better prognosis, while the opposite is the case for gastric carcinoma (GC) and ovarian cancer (17). In lung cancer, the relationship between USP13 expression and prognosis is associated with its pathological type. USP13 promotes the proliferation of small cell lung cancer (SCLC) (44). Epigenetic alterations in the *USP13* gene have been identified in certain cancers, such as hypermethylation in embryonal carcinomas of the testis (45). Several novel drugs such as JS-K have also been developed to target the epigenetic alterations of USP13 and benefit patients (46). USP13 is involved in the development of cancer by participating in several important signaling pathways, stabilizing the expression of specific proteins, regulating the repair of DNA damage, inhibiting glycolysis, activating glutamine catabolism and mediating chemoresistance to anti-cancer drugs (Fig. 2). Considering that USP13 functions differently in various cancers, its role remains to be further investigated in diverse tumors.

USP13 as a prognostic marker. USP13 is dysregulated in various tumors and can therefore be a good prognostic marker in tumors. USP13 has been shown to upregulate fatty acid synthase (FASN) to promote the proliferation of SCLC cells and Twist-related protein 1 (Twist1) to promote the migration and invasion of breast cancer cells, while it inhibits cell proliferation via downregulation of glycolysis in oral squamous cell carcinoma (47,48).

The regulatory role of USP13 in tumors is gradually being elucidated by current related research. Evidence has shown that USP13 primarily functions by interacting with various proteins and influencing the development of tumors. In different tumors, the expression of USP13 predicts different outcomes. For instance, in ovarian (49) and cervical cancer, high expression of USP13 predicts poor outcomes, while in oral squamous cell carcinoma, high expression of USP13 predicts good prognosis. The different roles of USP13 in the prognosis of tumors are listed in Table I. Owing to the complexity of its regulatory mechanism, the role of USP13 in making prognosis assessments in different cancers warrants further investigation (50).

USP13 signaling in cell proliferation and apoptosis
Targeting of AKT/MAPK signaling. USP13 promotes the proliferation of squamous cell lung carcinoma cells through AKT/MAPK signaling. Several studies have reported that the expression of PTEN and that of the apoptosis-inducing protein p53 is positively associated with USP13 (50-52). However,
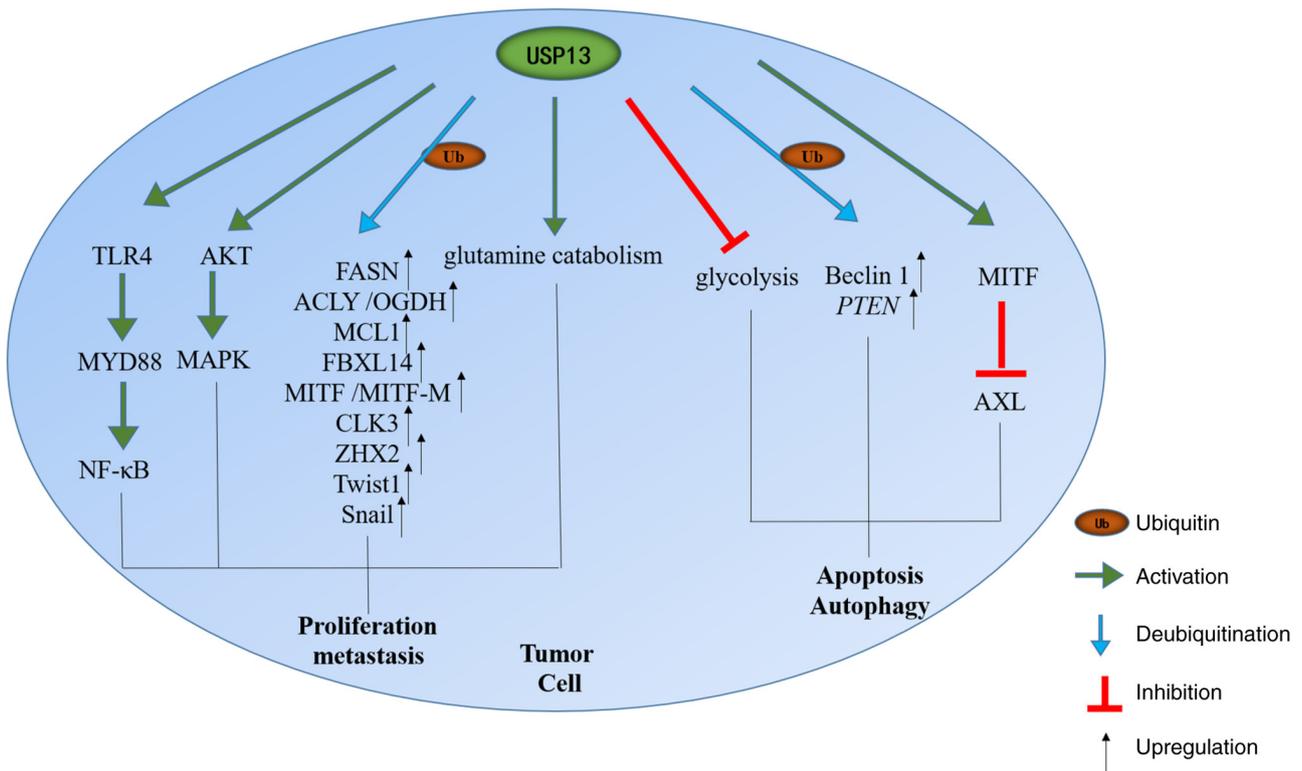
Figure 2. Role of USP13 in tumor progression. USP13, ubiquitin-specific protease 13; FASN, fatty acid synthase; ACLY, ATP citrate lyase; OGDH, 2-oxoglutarate dehydrogenase; MCL1, myeloid cell leukemia-1; FBXL14, F-box and leucine-rich repeat protein 14; MITF, microphthalmia-associated TF; CLK3, CDC-like kinase 3; ZHX2, zinc fingers and homeoboxes 2; Twist1, Twist-related protein 1; PTEN, phosphatase and tensin homolog; TLR, toll-like receptor; AXL, Anexelekto.

Wu *et al* (53) drew different conclusions, showing the expression of PTEN and p53 was independent of USP13.

Interaction with FASN. USP13 promotes the growth of SCLC cells by maintaining the expression of FASN through the ubiquitin-proteasome pathway. This process could be rescued by FASN inhibition (47).

Interaction with ATP citrate lyase (ACLY) and 2-oxoglutarate dehydrogenase (OGDH). There is a synergy between inhibiting the expression of USP13 and PI3K/AKT signaling in the treatment of ovarian cancer. ACLY and OGDH are closely related to acetyl-CoA formation, involved in the mitochondrial tricarboxylic acid cycle (54-56) and induction of cancer cell proliferation. ACLY and OGDH are substrates of USP13, and their expression decreases with USP13 knockdown. The USP domain of USP13 is essential for interaction with these substrates (49).

Regulation of glutamine catabolism. Glutamine catabolism is positively associated with the prognosis of various cancers (57,58). A total of 1/3 of patients with ovarian cancer show USP13 amplification. As it was aforementioned, USP13 deubiquitinates OGDH and ACLY. A USP13 deficiency therefore downregulates the expression of OGDH, thus, lactic acid accumulates and cell growth is inhibited. This process inhibits glutamine metabolism. ACLY participates in acetyl-CoA formation; therefore, USP13 depletion also inhibits glutamine catabolism and induces mitochondrial dysfunction, enhancing the sensitivity of ovarian cancer cells to AKT inhibitors (59).

Interaction with myeloid cell leukemia-1 (MCL1). MCL1 belongs to the BCL-2 family and is involved in the anti-apoptotic process by inducing the cell cycle (60). There is a positive association between the expression of USP13 and MCL1 in cancer. USP13 interacts with MCL1 and stabilizes its expression by deubiquitinating MCL1. The N-terminal of USP13 and MCL1 are necessary for this interaction, which is independent of the MCL1 ubiquitination. USP13 deficiency inhibits tumor cell growth; therefore the pharmacological targeting of USP13 is a potential treatment against tumors (61).

For instance, MCL-1 is expressed at high levels in cervical cancer and the expression of USP13 is independent of human papillomavirus infection (13). ABT-263, a small-molecule antagonist that inhibits the activity of the anti-apoptotic protein BCL-2 and BCL-XL, has no inhibitory effect on MCL-1. Therefore, the tumor cells expressing high levels of MCL-1 showed a reduced sensitivity to ABT-263 (62). USP13 knockdown downregulates the expression of MCL-1 and enhances the sensitivity of tumor cells to ABT-263. USP13 is also downregulated by the autophagy inducer C-JUN/AP-1, and inhibition of apoptosis-related MAPK/JNK signaling effectively downregulates the expression of USP13. Inhibition of USP13 renders cervical cancer cells sensitive to ABT-263 and benefits patients with high expression of MCL-1 (13).

Interaction with F-box and leucine-rich repeat protein 14 (FBXL14). FBLX14, an E3 ubiquitin ligase that belongs to the RING family, contains 11 leucine-rich repeats and an F-box motif, is involved in cancer progression, and functions as a cancer suppressor. FBLX14 stabilizes the expression of c-Myc, an important transcription factor (TF) involved in the regulation of the cell cycle, aging and differentiation (63).

Table I. USP13 as a prognostic marker in tumor.

First author/s, year	Tumor	USP13 expression	Target	Mechanism	Prognosis	(Refs.)
Wu et al, 2019	Squamous cell lung carcinoma	Upregulated	AKT/MAPK	Promoting cell proliferation	Poor	(53)
Wang et al, 2022	Small cell lung cancer	Upregulated	FASN	Promoting cell proliferation	Poor	(47)
Han et al, 2016	Ovarian cancer	Upregulated	ACLY and OGDH	Promoting cell proliferation	Poor	(49)
Han et al, 2018	Ovarian cancer	Upregulated	Glutamine catabolism	Promoting cell proliferation	Poor	(59)
Zhang et al, 2018	Cervical cancer	Upregulated	MCL1	Inhibiting cell apoptosis	Poor	(61)
Fang et al, 2017	Glioblastoma	Upregulated	FBXL14	Inhibiting cell apoptosis	Poor	(64)
Hu et al, 2021	Melanocytoma	Upregulated	MITF and MITF-M	Promoting cell proliferation	Poor	(66)
Zhou et al, 2020	Gastrointestinal cancer	Upregulated	CLK3	Reprogramming purine metabolism	Poor	(67)
Xie et al, 2022	Clear cell renal cell carcinoma	Upregulated	ZHX2	Promoting cell proliferation	Poor	(68)
Zhao et al, 2023	Breast cancer	Upregulated	Twist1	Promoting migration and invasion	Poor	(79)
Zhang et al, 2022	Gastric cancer	Upregulated	Snail	Promoting migration and invasion	Poor	(80)
Gao et al, 2020	Hepatocellular carcinoma	Upregulated	TLR4/MYD88	Promoting migration and invasion	Poor	(81)
Man et al, 2019	Bladder cancer	Downregulated	NF-κB	Inhibiting migration and invasion	Well	(84)
Zhang et al, 2013	Breast tumor	Downregulated	PTEN	Inhibiting cell proliferation	Well	(51)
Qu et al, 2019	Oral squamous cell carcinoma	Downregulated	Glycolysis	Inhibiting cell proliferation	Well	(50)

USP13, ubiquitin-specific protease 13; FASN, fatty acid synthase; ACLY, ATP citrate lyase; OGDH, 2-oxoglutarate dehydrogenase; MCL1, myeloid cell leukemia-1; FBXL14, F-box and leucine-rich repeat protein 14; MITF, microphthalmia-associated TF; CLK3, CDC-like kinase 3; ZHX2, zinc fingers and homeoboxes 2; Twist1, Twist-related protein 1; PTEN, phosphatase and tensin homolog; TLR, toll-like receptor.

High expression of c-Myc has been identified in numerous types of cancers and is associated with poor prognosis. As a proto-oncogene, c-Myc is important in cell growth and apoptosis. Post-translational modifications, especially ubiquitination and deubiquitination, play an important role in the regulation of c-Myc. Fang et al (64) reported that USP13 is a potential marker of glioma stem cells. USP13, FBXL14 and c-Myc can interact with each other; USP13 inhibits the degradation of c-Myc, hence inhibition of USP13 promotes the apoptosis of glioma stem cells. By contrast, overexpression of FBLX14 induces the differentiation of glioma cells and inhibits their growth. USP13 and FBXL14 regulate the expression of c-Myc via ubiquitination and deubiquitination respectively, influencing the fate of glioma cells.

Interaction with microphthalmia-associated TF (MITF) and MITF-M. MITF is a member of the helix-loop-helix-leucine zipper TF family that induces the proliferation of cells and is a key factor in the development of melanocytoma. MITF induces cell-cycle arrest and upregulates the transcription of major pigmentation enzymes such as tyrosinase in the development of melanocytoma. USP13 binds to MITF and cleaves the ubiquitin chain (65).

MITF-M is an isoform of MITF. MITF-M is activated by Wnt signaling and promotes melanocyte proliferation. USP13 interacts with MITF-M and stabilizes its expression, thereby notably influencing the generation of melanocytoma (66).

Interaction with CLK3. CLK3 is a nuclear dual-specificity kinase that takes part in RNA splicing by phosphorylating serine/arginine-rich proteins. CLK3 interacts with USP13, phosphorylates it at the Tyr708 residue and inhibits the ubiquitination of c-Myc to activate c-Myc-mediated purine biosynthesis, thus promoting the progression of bile duct cell carcinoma (67).

Interaction with zinc fingers and homeoboxes 2 (ZHX2). USP13 influences the deubiquitination of transcriptional repressor ZHX2 to maintain its stability. ZHX2 inhibits the expression of multiple genes and acts as a tumor suppressor in various tumors such as gastric cancer. As a result, NF-κB

signaling is activated, which in turn induces the development of clear cell renal cell carcinoma (ccRCC). Thus, the depletion of USP13 decreases ZHX2 and inhibits the proliferation of ccRCC (68).

Interaction with Vps34 complex. Defects in autophagy in tumor cells affect the stability and survival of tumor cells. Vps34, a unique member of the class III phosphoinositide 3-kinase, is an autophagy-associated protein that controls autophagosome generation, and its ubiquitination is downregulated by the NEDD4-USP13 complex. NEDD4-1 recruits USP13 to form a NEDD4-USP13 complex, thereby increasing the interaction between USP13 and Vps34 and inhibiting K48-linked ubiquitination of Vps34 on K419. This interaction stabilizes the expression of Vps34 and positively regulates autophagy (69).

Beclin 1 is a part of the Vps34 complex (70,71). USP13 interacts with Beclin 1 and stabilizes its expression, further regulating the expression of the Vps34 complex and p53.

The Vps34 complexes can upregulate their expression by stabilizing the interaction between USP13 and Beclin 1, which in turn upregulates the expression of Beclin 1 by deubiquitination. The regulation of deubiquitination of Beclin 1 is sufficient to maintain the level of Vps34 complexes. The C-terminus of Beclin1 is necessary for this interaction (52).

Interaction with PTEN. PTEN negatively modulates PI3K signaling and acts as a tumor suppressor (72). PTEN is downregulated in a number of tumors such as non-SCLC, and its expression is regulated by the ubiquitin-proteasome system (73,74). E3 ubiquitin ligase WW domain-containing E3 Ub-protein ligase 2, carboxyl-terminal of Hsp70-interacting protein and NEDD4-1 target PTEN for degradation.

USP13 interacts with PTEN, stabilizes its expression through deubiquitination and further downregulates AKT signaling to inhibit the proliferation of tumor cells. The phosphatase domain of PTEN is required for this interaction, which is a post-translational modification; thus, the expression of PTEN at the mRNA level and its location are not changed by USP13 (51,75).

Regulation of glycolysis. Energy is mainly provided through glycolysis in tumor cells under sufficient oxygen and this known as the Warburg effect (76). Changes in glycolysis are a hallmark of tumorigenesis and are associated with cancer prognosis (77).

USP13 deficiency promotes glucose uptake and glycolysis (51). microRNA (miR)-135B downregulates USP13 to regulate PTEN levels via post-translational modification, and promote glycolysis and cell proliferation in colorectal cancer (78).

In addition, the expression of USP13 is decreased in oral squamous cell carcinoma, while its overexpression effectively inhibits the proliferation of tumor cells and the Warburg effect through PTEN/AKT signaling (50).

USP13 signaling in tumor metastasis
Interaction with Twist1. Twist1 is an important TF involved in the epithelial-to-mesenchymal transition (EMT) process. In this process, tumor cells gain the ability to invade and migrate. High expression of Twist1 is closely associated with the invasion and migration of tumors (48). While the expression of Twist1 could be regulated by USP13, USP13 interacts with Twist1 and

stabilizes its expression via the ubiquitin-proteasome pathway. High expression of USP13 promotes the migration and invasion of tumors such as breast cancer through Twist1 (79).

Maintaining the stability of Snail. Snail directly inhibits the transcription process of E-cadherin, a tumor invasion suppress related molecular, and acts as a critical driver of EMT and metastasis of GC. USP13 promotes migration and invasion of GC cells by maintaining the stability of Snail. High expression of USP13 is associated with poor differentiation and high aggression, which predicts poor prognosis of GC (80).

Targeting toll-like receptor (TLR)4/MYD88 signaling. USP13 stabilizes the expression of genes downstream of TLR4/MYD88 signaling and is associated with an unfavorable prognosis in hepatocellular carcinoma (HCC). USP13 knockdown increases TLR4 ubiquitination, leading to its decreased expression, which results in the decreased expression of MYD88, phosphorylated-NF-κB and p65, thus inhibiting the proliferation and invasion of HCC cells. By contrast, USP13 expression induced by hypoxia activates TLR4/MYD88/NF-κB signaling and promotes cell proliferation (81).

Targeting NF-κB pathway. NF-κB upregulates the expression of the oncogene miR-130b, which acts directly on USP13, decreasing its expression and thereby regulating the proliferation, invasion and migration of tumor cells. Therefore, it is a potential target for cancer therapeutics (82,83). miR-130b/miR-301b binds to USP13 via the 3'-UTR. In bladder cancer, the expression of miR-130b is negatively associated with the expression of USP13. Restoring USP13 levels partially inhibits the invasion and migration of tumor cells by stabilizing the expression of PTEN (84).

Taking part in the miRNA-539-3P/USP13/MITF/AXL axis. The androgen receptor is important for the regulation of the miRNA-539-3P/USP13/MITF/AXL axis and induces the degradation of MITF via the ubiquitin-proteasome pathway, further increasing the expression of receptor tyrosine kinase AXL to promote melanoma metastasis. USP13 plays an important role in regulating MITF degradation. The 3'UTR of USP13 can be directly targeted by miRNA-539-3P. Androgen receptors decrease the expression of USP13 by upregulating miRNA-539-3P, thus increasing the degradation of MITF protein by ubiquitination and promoting melanoma metastasis (85,86).

USP13 signaling in chemoresistance
Mediating afatinib resistance. Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that regulates cellular proliferation and is a potential target for cancer therapies. EGFR inhibitors have shown a beneficial effect on lung and colorectal cancer, among other cancers such as glioblastoma. However, resistance to EGFR inhibitors remains a major challenge (87,88). A total of 1/3 of patients with non-SCLC have mutations in the EGFR kinase domain. The ΔE746-A750 and L858R mutations of EGFR are associated with the sensitivity to EGFR inhibitors, such as afatinib, and upregulate kinase activity. USP13 binds more tightly to the mutant EGFR than to wild-type EGFR. USP13 inhibits the degradation of mutant EGFR via deubiquitination, binds to mutant EGFR via its UBA domains, and inhibits EGFR endosomal sorting and lysosomal degradation. The E3 ubiquitin ligase c-cbl is important in this regulatory process.

USP13 knockdown enhances the sensitivity of tumor cells to afatinib (89).

Inducing imatinib resistance. Imatinib resistance remains a major challenge in the treatment of gastrointestinal stromal tumors (GIST) and one of the reasons is protective autophagy (90). As a notable marker of autophagy, USP13 interacts and downregulates the polyubiquitylation of autophagy-related protein 5 to induce resistance to imatinib in GIST. The serine/threonine protein kinase p21-activated kinase 1 promotes this interaction process. USP13 can be modified by methyltransferase-like 3 to maintain its stability by enhancing m^6A methylation (91).

Regulating DNA repair. BRCA1 mainly functions in maintaining genome stability and regulates DNA damage response by promoting homologous recombination. Numerous factors are involved in the process of DNA repair. Histones and other proteins in the damage site are ubiquitinated, the K63 linked polyubiquitin chain acts as an anchor site for the key DNA damage response regulator receptor-associated protein 80 to recruit BRCA1, and the complex further facilitates the DNA damage response. USP13 regulates DNA damage response by interacting with RAP80 to deubiquitinate it and promote the formation of the RAP80-BRCA1 complex. K75, K90, and K112 residues of RAP80 are the main deubiquitination sites. The interaction between RAP80 and the K63-linked polyubiquitin chain is increased when RAP80 is deubiquitinated by USP13, which is crucial for its recruitment to DNA damage sites and the formation of the RAP80-BRCA1 complex. The generation of the RAP80-BRCA1 complex decreases with USP13 knockdown. Additionally, ATM phosphorylates USP13 at Thr196, which is important for the recruitment of USP13 to double-strand breaks and the induction of DNA damage. Via the regulation of the formation of the RAP80-BRCA1 complex, USP13 takes part in DNA damage response and induces resistance to chemotherapy in ovarian cancer (92).

USP13 inhibitor in cancer therapy. Spautin-1 is an inhibitor of autophagy that inhibits USP13 and 10 expression, and has been used in the treatment of chronic myeloid leukemia, and ovarian and lung cancer (93). In addition, Spautin-1 is also effective in the F508 deletion mutant of the ATP-bound transmembrane protein cystic fibrosis transmembrane conductance regulator. It mainly influences the expression of cell cycle arrest related protein growth arrest and DNA-damage-inducible protein 45 α/β and G2/M cell cycle checkpoint regulator STRATIFIN, thereby affecting the cell cycle and inducing apoptosis. Spautin-1 upregulates reactive oxygen species (ROS)-mediated DNA damage and induces G2/M cell cycle arrest and apoptosis. USP13 is upregulated in melanoma; Spautin-1 inhibits the growth of melanoma cells *in vitro* without visible toxicity to normal cells. The combination of Spautin-1 with platinum-based drugs such as cisplatin has shown a synergistic effect in melanoma treatment (93).

Novel inhibitors of USP13, such as BK50118, are also under investigation. These drugs show distinct advantages; some of them for examples can cross the blood-brain barrier to reach the cerebrum, thus benefiting patients with neurodegeneration via reduction of neurotoxic protein by attenuating the deubiquitination of neurotoxic proteins (94).

In conclusion, USP13 either promotes or inhibits the development of different tumors. Its expression is associated with the prognosis of patients. Targeting USP13 for cancer treatment is of interest because of its involvement in regulating tumor suppressors or oncoproteins in a post-translational manner. Therefore, it is necessary to study its function in different tumors and different groups of people to draw accurate conclusions.

The difference in the expression of USP13 in various tumors can be used in treatment. USP13 inhibitors such as spautin-1 and BK50118 are also potential candidates in the treatment of cancer.

6. Conclusions

USP13 is widely expressed in different cancer cells, such as lung, ovarian and breast cancer cells, and influences tumor progression in an enzymatically dependent or independent manner (43). As a notable post-translational modification, the role of deubiquitination in physiological and pathological processes has been explored (95). USP13 is involved in different diseases such as inflammation and tumor by participating in important cellular signal transduction pathways and by downregulating the degradation of target proteins. Thus, it has become a research hotspot in pathophysiology including inflammation and tumor formation (96,97). However, the role of USP13 in the formation and progression of tumors is complex. USP13 participates in various physiological processes in tumor cells, such as glycolysis and glutamine catabolism, and in the growth and metastasis of tumors by regulating the stability of various proteins. Owing to the complexity and variety of the proteins involved in the regulation process, USP13 plays different roles in various diseases, especially in cancer. Though most evidence showed that USP13 promoted the development of cancer, it has also been reported to inhibit some tumors, such as oral squamous cell carcinoma; however, the underlying mechanism warrants further exploration. These discrepancies may be attributed to ethnicity differences, small sample size and different detection methods. Furthermore, whether the function of USP13 in tumors is associated with its enzymatic activity remains to be determined. USP13 regulates DNA repair, senescence and proteasomal degradation via interactions with RAP80-BRCA1 complex, cell senescence related E3 ubiquitin ligase murine double minute 2 (MDM2) and inflammation regulation-associated protease inactive rhomboid protein 2 (IRHOM2), respectively, and via hydrolyzation of K63-linked ubiquitin chains (67,92). USP13 is also involved in the cleavage of K48-linked polyubiquitin chains in some cases, such as the upregulation of Twist1 (79). The regulatory function of USP13 in hydrolyzing different types of ubiquitin chains is complex and it may affect the tumor progression. Though its deubiquitination activity is limited, it has been reported that the effects of USP13 in tumors depend on its interaction with proteins such as PTEN and Twist1. Specific inhibitors of USP13 are also under investigation. Spautin-1 inhibits USP13 expression, but the effect is not specific; its role in the treatment of diseases deserves further investigation. Understanding the role of USP13 in various diseases will help to facilitate the development of therapeutic interventions.

Availability of data and materials

Not applicable.

Authors' contributions

XM and SH contributed to the conceptualization of the current study and gave constructive guidance. YT and XX collected the relevant studies and wrote the manuscript. RS participated in the design of the present review. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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