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Review article

Emerging role of ubiquitin-specific protease 14 in oncogenesis and development of tumor: Therapeutic implication

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ABSTRACT

Ubiquitin (Ub) is a small protein that can be attached to substrate proteins to direct their degradation via the proteasome. Deubiquitinating enzymes (DUBs) reverse this process by removing ubiquitin from its substrate protein. Over the past few decades, ubiquitin-specific protease 14 (USP14), a member of the DUBs, has emerged as an important player in various types of cancers. In this article, we review and summarize biological function of USP14 in tumorigenesis and multiple signaling pathways. To determine its role in cancer, we analyzed USP14 gene expression across a panel of tumors, and discussed that it could serve as a novel bio-marker in several types of cancer. And recent contributions indicated that USP14 has been shown to act as a tumor-promoting gene via the AKT, NF-κB, MAPK pathways etc. Besides, drugs targeting USP14 have shown potential anti-tumor effect and clinical significance. We focus on recent studies that explore the link between USP14 and cancer, and further discuss USP14 as a novel target for cancer therapy.

1. Introduction

Eukaryotic cells employ two major proteolytic systems: the ubiquitin-proteasome system (UPS) and the autophagy-lysosome system, which accounts for approximately 80–90% and 10–20% of cellular proteolysis respectively [1,2]. The UPS is a selective proteolytic system in which the conjugation of ubiquitin to substrates induces degradation by the proteasome [3]. Autophagy is an evolutionarily conserved, bulk degradation pathway whereby long-lived proteins and whole organelles are delivered to lysosomes for breakdown [4]. The core of both degradation pathways is ubiquitination, which generates linkage-specific degrons on substrates destined for destruction [1]. Ubiquitin modifications are added to substrate lysine residues by the E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme cascade and E3 ubiquitin ligase, resulting in the formation of a covalent isopeptide bond between the C-terminus of ubiquitin and a nucleophilic group on the substrate [5]. DUBs remodel and remove conjugated ubiquitin chains from substrate proteins, rescuing them via degradation or modulating Ub-mediated signal transduction [6,7]. Moreover, deubiquitylation is important for ubiquitin homeostasis as it prevents degradation of ubiquitin and recycles ubiquitin back to the free ubiquitin pool [8].

The proteasome most exclusively used in human is the 26S proteasome (molecular mass 2000 kDa), which consists of one 20S protein subunit and two 19S regulatory cap subunits (Fig. 1) [9]. Up until now, two types of subunits of 26S proteasome have attracted considerable attention in the field of cancer research. Due to the importance of protein degradation in cell survival, the 26S proteasome has been a prime focus in cancer research. For example, two drugs that target the 20S subunit, bortezomib and ixazomib, had been approved for treating hematological malignancies by the United States Food and Drug Administration (FDA) [10]. Three proteasome-associated DUBs located in 19S regulatory complexes, USP14, Ub carboxyl-terminal hydrolase isozyme L5 (UCHL5) and RPN11, could remove conjugated ubiquitin chains [11].

Accumulating evidences implicated that USP14 was overexpressed in several cancers, including colorectal cancer, non-small-cell lung cancer, ovarian cancer as well as esophageal squamous cell carcinoma [12–15], and participated in multiple signaling pathways to regulate cell proliferation, apoptosis, autophagy and ets. of cancer cells [16–18]. Besides, USP14 inhibitors have shown potential anti-cancer effects [19,20]. These efforts suggest that USP14 plays a critical role in oncogenesis and development of tumor, and propose a possibility that development of USP14 inhibitors can be considered an interesting therapeutic target for treatment of cancer.

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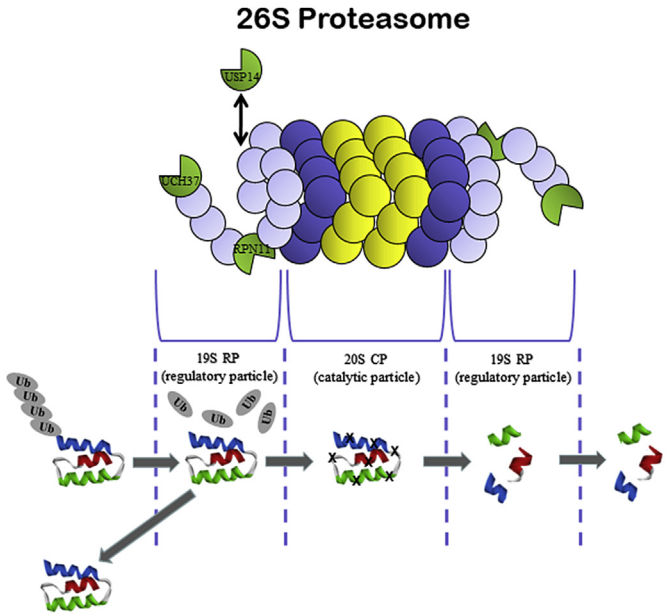


Fig. 1. The structure and function of 26S proteasome. The 26S proteasome consists of two 19S regulatory particles and one 20S catalytic particle. Three DUBs (USP14, UCH37 and RPN11), located at the 19S complexes, are responsible for disassembling the association between ubiquitin and its substrate protein. When a Ub-tagged protein is transported to proteasome, Ub first could be dissociated from the substrate in 19S particle. Then, the substrate either leaves the 26S proteasome, or it could be catalytic into 20S core and discharged to cytoplasm.

2. The deubiquitination enzymes

There have been around 100 DUBs found in human, each with distinct substrate specificities and enzymatic properties, which show remarkable specificity for cracking different multiple chain types [21,22]. Based on their catalytic mechanisms, DUBs can be broadly divided into two classes: cysteine proteases and metalloproteases. The cysteine protease DUBs, the more common of the two classes, consists of four subclasses based on their Ub-protease domains: ubiquitin-specific proteases (USPs), ubiquitin C-terminal hydrolases (UCHs), ovarian tumor proteases (OTUs), and Machado-Joseph disease proteases (MJDs) [23]. The metalloprotease class contains only the Jab1/Mov34/Mpr1 Pad1 N-terminal+ (MPN+) (JAMM) domain proteases. Table 1 shows the information of different types of DUBs including DUB subfamily, representative DUBs, cancer type and tumorigenesis of each DUB. The USP is the largest family of DUBs, with over 50 members [7]. The catalytic domain of USPs contains two short and well-conserved motifs, called the Cys and His boxes, which include the critical residues for catalysis [24]. Among the three DUBs associated with mammalian proteasome, USP14 is research hotspot because it negatively regulates proteasome activity by ubiquitin chain disassembly as well as by a noncatalytic mechanism [25–29]. We will explore the interplay between USP14 and the proteasome below.

3. USP14 and 26S proteasome

The 26S proteasome is an ATP-dependent and multi-subunit protease that primarily degrades ubiquitinated proteins. The proteasome holoenzyme is composed of a 19-subunit regulatory particle (known as the RP, 19S complex, or PA700) and a 28-subunit core particle (known as the CP, or 20S complex) [27]. A substrate first binds the RP, then is actively translocated to the CP for degradation. The three DUBs associated with the 19S proteasome lid complex, Rpn11, UCHL5, and USP14, are all present at $> 4 \times 10^5$ copies per cell, which is consistent with other proteasome subunits [8]. Unlike the two other DUBs, USP14 interaction with 19S complex is reversible [30]. Mammalian USP14 contains a ubiquitin-like (Ubl) domain at the N-terminus, which is responsible for the reversible association with 26S proteasomes [8,31]. In the absence of ubiquitin binding, the active site of USP14, which consists of three amino acid residues (C114, H435 and D451), is blocked by the two surface loops BL1 and BL2. Upon ubiquitin binding, BL1 and BL2 undergo conformational changes to relieve the autoinhibition and activate USP14 [32]. The confirmation changes of loops BL1 and BL2 were illustrated in a structure diagram of USP14 in Fig. 2 by Worldwide Protein Data Bank database [33] and PyMOL software.

USP14 can be activated by the 26S proteasome. Borodovsky A et al. demonstrated an increased USP14 activity when proteasome function is impaired, suggesting functional coupling between the activities of USP14 and the proteasome [34]. Studies by Ponnappan et al. also showed that a compensatory increase in USP14 activity is induced when the activity of the 26S proteasome declines during aging [35].

USP14 can reciprocally regulate the activity of the 26S proteasome. USP14 was previously reported to inhibit protein degradation by catalyzing substrate deubiquitination [36]. Occupancy of USP14's active site by a ubiquitinated substrate or an inhibitor of deubiquitination activated proteasomal degradation via enhancing 20S gate opening [28,37]. The similar results occurred when substrate-protein was co-incubated with purified 26S proteases [27,28]. Goldberg's group further characterized the effect of USP14 on 26S proteasome. They reported that USP14 has seemingly opposite actions and that it functions both as an inhibitor and an activator of proteolysis. In the absence of a substrate, USP14 maintains the 26S proteasomes in a quiescent state, decreasing nonspecific degradation of non-ubiquitinated proteins. However, upon binding a Ub conjugate, USP14 allosterically activates several enzymatic processes that enhances ATPase activity and DUB activities, resulting in an increase in specificity for ubiquitinated substrates [38]. These studies demonstrate that USP14 serve as a central regulator of the 26S proteasome.

4. USP14 and cancer

As an important member of the ubiquitin proteasome system, USP14 has been received significant attention for its crucial role in various cancers. Using the UALCAN database, we analyzed gene expression data of USP14 in primary tumor and stage 1–4 tumor in human patients with different types of cancer (Fig. 3) [39]. The figure can be divided into two parts, of which the upper part means that USP14 probably acts as an oncogene or exerts a tumor-promoting role in corresponding tumors, while the lower represents that USP14 may not act tumor-promoting role in those tumors. Specifically, USP14 probably plays the tumor-promoting role in approximately 61% cancers (19 of 31 types of cancer). We found a close correlation between USP14 gene and a majority of cancers. USP14 gene is highly expressed in breast invasive carcinoma, colon adenocarcinoma and lung squamous cell carcinoma. On the other hand, USP14 gene expression positively correlates with stages of tumor progression in adrenocortical carcinoma, cervical squamous cell carcinoma, and head and neck squamous cell carcinoma.

In recent years, an increasing number of studies have reported the significance of USP14 in cancer. Researchers have investigated its stimulatory effect on cell growth, migration, kinase activation and the activation of the inflammasome, as well as its inhibitory effect on cell autophagy and apoptosis in cancer cells (Fig. 4). In 2006, Shinji S et al. found that USP14 expression significantly correlates with tumor pathological stage, and lymph node, as well as liver metastases. Moreover, USP14 expression in colorectal tumors negatively predicts patients' survival rate [12]. Li and colleagues also highlighted the role of USP14 in non-small cell lung cancer. Abnormal high-expression of USP14 was detected in NSCLC patients and cell lines, and associated with poor prognosis in NSCLC patients. On the other hand, silencing of USP14 suppressed tumor cell proliferation via reduction of β-catenin [13]. Wu et al. identified a negative correlation between USP14 mRNA level and

Table 1
Representative DUBs and associations with cancer.

DUB subfamily	Representative DUBs	Cancer type	Tumorigenesis	Reference
Ubiquitin-specific protease (USP)	USP1	Osteosarcoma	Promote cell growth and invasion of osteosarcoma	[91]
		Ovarian cancer	Mediate cancer cell resistance to platinum and promote tumor dissemination	[92]
		Breast cancer	Promote cell migration, invasion and cancer metastasis	[93]
	USP7	Prostate cancer	Be associated with PTEN nuclear exclusion	[94,95]
		Non-small cell lung cancer	Stabilize p53 and induce p53-dependent cell growth repression and apoptosis	[96,97]
	USP22	Liver cancer	Genetic depletion of USP22 inhibits liver cancer cell growth	[98]
		Colorectal cancer	Regulate CCND1 stability to control cell cycle progression	[99]
		Lung adenocarcinoma	Promote cell proliferation, migration and invasion of lung adenocarcinoma	[100]
		Leukemia	Be linked to cancer progression	[101]
Ubiquitin C-terminal hydrolase (UCH)	UCHL5	Gastric cancer	Positive cytoplasmic UCHL5 tumor expression is linked to improved prognosis	[102]
		Lung cancer	Promote cancer cell apoptosis	[103]
		Pancreatic carcinoma	Impair cell migration	[104]
	BAP1	Lung cancer	Suppress the growth of lung cancer cell	[105–107]
		Mesothelioma	Germline BAP1 mutations lead to malignant mesothelioma	[108]
		Colorectal cancer	Reduced BAP1 expression is associated with poor prognosis of colorectal cancer	[109]
Machado-Joseph disease protease (MJD)	JOSD1	Gynaecological cancer	JOSD1 depletion leads to severe apoptosis both in vivo and in vitro	[110]
	ATXN3	Breast cancer	Enhance tumor formation and correlate with poor prognosis	[111]
		Lung cancer	Decrease cell viability of lung cancer	[112]
Ovarian tumor protease (OTU)	OTUB2	Non-small cell lung cancer	Promote cell growth, migration and invasive activity of non-small cell lung cancer	[113]

Abbreviations: USP1: Ubiquitin-specific protease 1; USP7: Ubiquitin-specific protease 7; USP22: Ubiquitin-specific protease 22; UCHL5: Ubiquitin carboxyl-terminal hydrolase isozyme L5; BAP1: BRCA1-associated protein 1; JOSD1: Josephin domain-containing protein 1; ATXN3: Ataxin-3; OTUB2: OTU domain-containing ubiquitin aldehyde-binding protein.

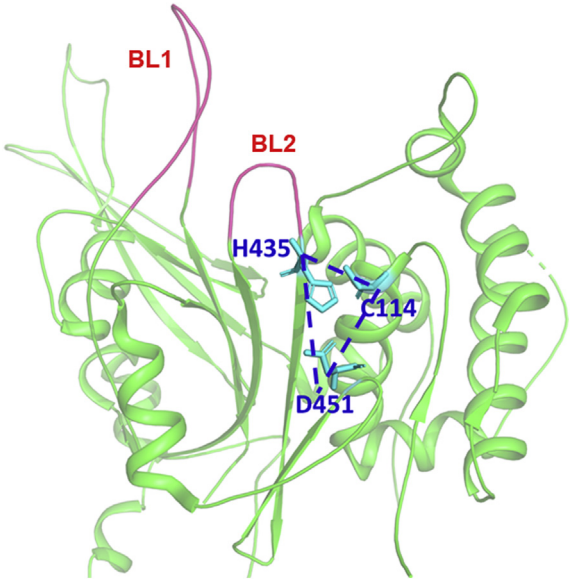


Fig. 2. The structure of USP14. When ubiquitin binding is absent, the active site of USP14 (consisting of C114, H435 and D451) is covered by the loops BL1 and BL2; when ubiquitin is binding, BL1 and BL2 undergo conformational changes to relieve the autoinhibition and activate USP14.

miR-4782-3p level. Moreover, it was shown that miR-4782-3p could inhibit cell growth in NSCLC by targeting USP14 [40]. Similar findings were echoed in epithelial ovarian cancer (EOC). The protein level of USP14 in EOC tissues was reported to be higher than that in normal ovarian tissues, and USP14 overexpression was associated with poor prognosis in EOC patients. Meanwhile, knockdown of USP14 led to cell growth repression and excessive apoptosis in EOC cells [17]. In 2009, Wada et al. conducted focus formation assays using retroviral expression libraries of ovarian cancer cell lines, and identified USP14 as an ovarian-cancer related oncogene with high transforming potential, and the outcome of which indicated that USP14 was closely related to the formation of ovarian cancer [41]. Additionally, Huang et al. demonstrated that USP14 was up-regulated in tumor tissues of patient with hepatocellular carcinoma (HCC) using qPCR and immunohistochemical techniques. More importantly, knockdown of USP14 suppressed cell proliferation, altered the cell cycle, and induced cell apoptosis. These findings showed that USP14 played an oncogenic role in promoting tumor progression in HCC [42]. Similarly, high mRNA and protein expression of USP14 in esophageal squamous cell carcinoma, suggesting that USP14 significantly relates to distant metastasis [43]. These studies concluded that high expression of USP14 is associated with poor prognosis in cancer [12,13,17,40].

The mechanism of USP14 in tumorigenesis have been extensively investigated. Mines et al. found that USP14 could induce deubiquitination of CXCR4, thus facilitating its degradation [44]. Another research team discovered that USP14 deubiquitinated K63-linked polyubiquitin chains of Dvl, and USP14 inhibition could attenuate Wnt signal transduction [45]. In leukemia, USP14 also played a pivotal role in regulating chemotherapy drugs-induced apoptosis by preventing Aurora B (a mitotic checkpoint kinase) to degrade [46]. Furthermore, in androgen-responsive prostate cancer cells, inhibiting the function of USP14 resulted in cell proliferation inhibition and cell cycle arrest at the G0/G1 phase, as USP14 could promote cell cycle by deubiquitination and stabilization of androgen receptor [47].

Inflammation is characterized by acute or chronic dysregulation of the host immune response, and it is a common manifestation of many diseases, including lung injury, osteoarthritis and myocarditis [38,48–50]. USP14 was found to regulate various signal transduction pathways, such as NF-κB pathway and the mitogen-activated protein kinase (MAPK) pathway, in response to inflammation [51,52]. Findings by Mialki et al. indicated that USP14 removes the ubiquitin chain of I-κB, thus triggering I-κB degradation and cytokine release in lung epithelial cells [51]. In ataxia mice, the loss of USP14 increased the levels of phosphorylated MAPKs, including phosphor-JNK and ERK [52]. As evidenced in a study by author et al., USP14 regulated the stability of CBP (cAMP response element-binding protein) by reducing its

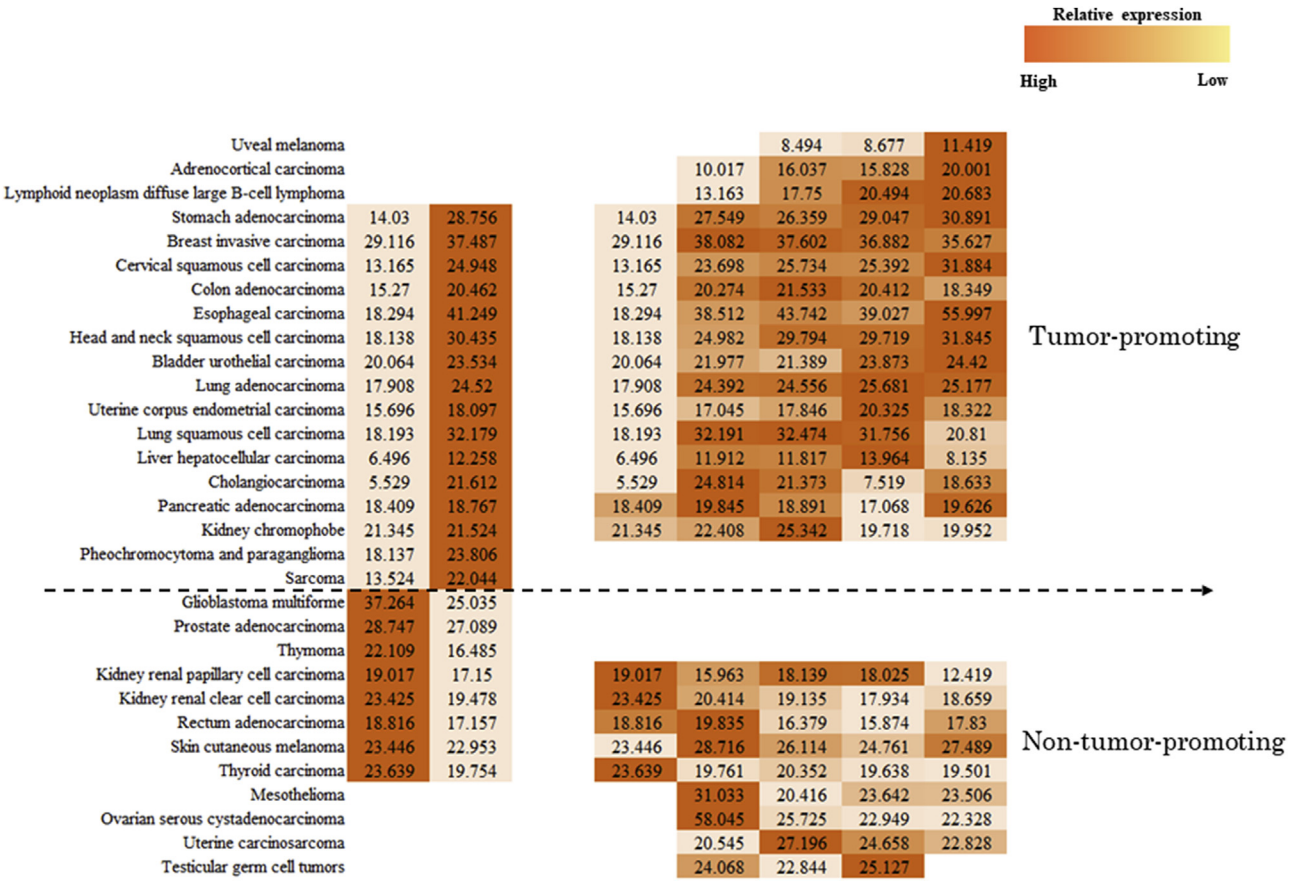


Fig. 3. USP14 gene expression in different types of human cancers. The considerable data of normal and tumor tissues is analyzed in 31 kinds of cancers. And the number represents relative expression of USP14 gene. In every line, darker red means higher expression of USP14 gene. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

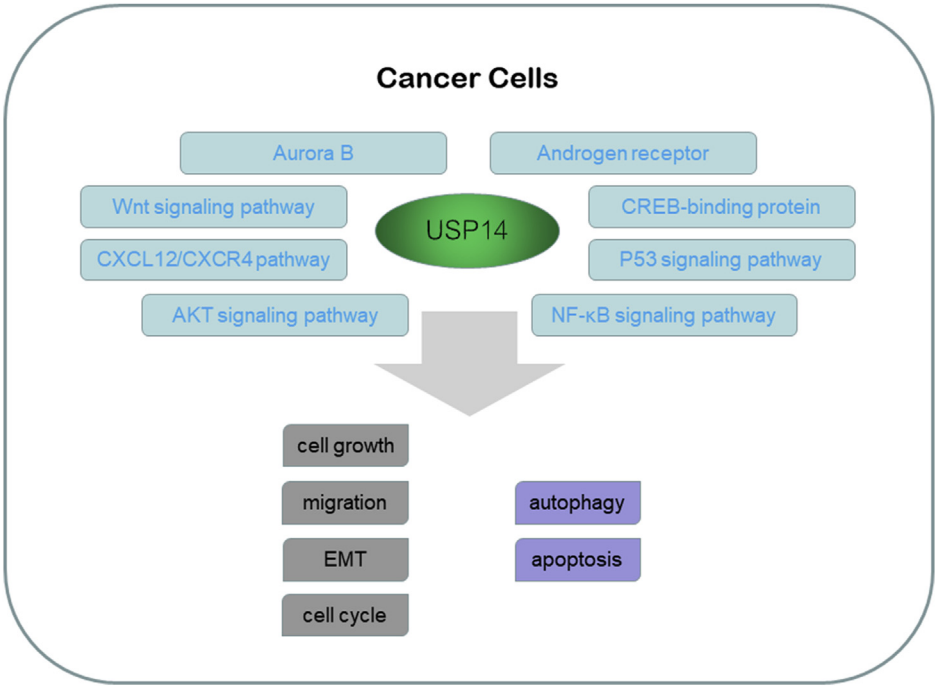
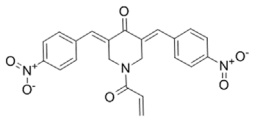
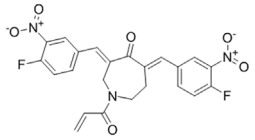
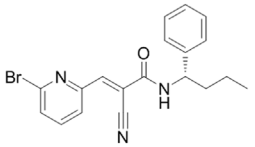
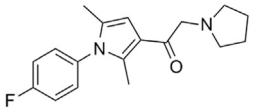
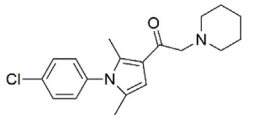
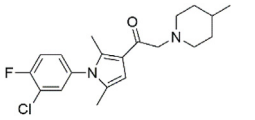
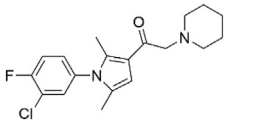
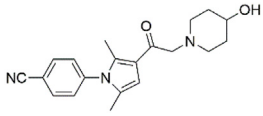


Fig. 4. The mechanism of USP14 in cancer. USP14 participates in multiple signaling pathway. In cancer cells, USP14 promote cell growth, migration, EMT and cell cycle, while repressing autophagy and apoptosis.

Table 2
Reported inhibitors targeting USP14.

USP14 inhibitor	Target	Structure	IC50	Reference
b-AP15	UCHL5, **USP14**		2.1 μM	[19,70,72]
VLX1570	UCHL5, **USP14**		10 μM	[75,77,78]
WP1130	USP9x, USP5, **USP14**, UCH37		N.A.	[79,80,114]
IU1	**USP14**		4–5 μM	[27,87,115]
IU1-47	**USP14**		0.6 μM	[85]
1D18	**USP14**		N.A.	[86]
1B10	**USP14**		N.A.	[86]
IU1-248	**USP14**		0.83 μM	[87]
miR-4782-3p	**USP14**	UGAUUGUCUUCAUAUCUAGAAC	N.A.	[40,88]

Note: N.A.: not available.

ubiquitylation, which lead to modulation of histone acetylation and lung inflammation [53].

Vimentin, a typical biomarker of the epithelial to mesenchymal transitions (EMTs) during embryogenesis and metastasis, has garnered widespread attention recently [54]. A recent study revealed that USP14 could interact with vimentin, and USP14 upregulation decreased the levels of ubiquitinated vimentin in human gastric cancer cell lines [55]. Moreover, USP14 knockdown inhibited the breast cancer cell migration by increasing the vimentin expression while reducing the E-cadherin expression, which suggested that USP14 affects breast cancer cell migration by targeting EMT [56].

It was reported that AKT-mediated phosphorylation of USP14 at Ser432 activated its deubiquitinating activity for both K48 and K63 ubiquitin linkages, thus regulating protease activity and consequently global protein degradation [57]. Interestingly, another study showed that USP14 regulates autophagy by negatively regulating K63 ubiquitination of Beclin 1 [58]. The authors proposed that activation of USP14 by AKT-mediated phosphorylation provides a mechanism for AKT negatively regulates autophagy by promoting K63 deubiquitination.

Besides, emerging studies have shown that USP14 plays a critical role in the drug resistance of tumors. Fu et al. found that USP14 could contribute to cisplatin resistance through Akt/ERK signaling pathways [59], and the study by Xu et al. indicated that USP14 promoted cell adhesion-mediated drug resistance through enhancing the ability of cell adhesion via Wnt-signaling pathways in multiple myeloma cells [60].

In conclusion, all of the aforementioned research offers us a brand-new insight into USP14's regulation in both proteasomal and autophagic degradation.

5. The inhibitors of USP14

The 26S proteasome is comprised of one 20S catalytic particle and two 19S regulatory particle [61,62]. The former contains multiple proteolytic sites, and the latter contains multiple ATPases and a binding site for ubiquitin concatemers [63,64]. The 20S catalytic subunit has been a successful target in the cancer therapy, and some of its inhibitors including bortezomib and ixazomib have been approved by FDA [10]. The 19S regulatory component (including USP14, UCHL5 and RPN11) has also attracted worldwide attention owing to its potential function in tumorigenesis [65–67]. Table 2 summarizes some known inhibitors that target USP14.

According to two studies from Linder group, b-AP15 was identified to induce the lysosomal apoptosis pathway in a screen for compounds [68,69]. The mechanism of b-AP15 is under active investigation. As the

dual inhibitor of UCHL5 and USP14, b-AP15 could result in accumulation of polyubiquitin, with P53- and BCL2-independent tumor cell apoptosis. Moreover, b-AP15 showed a significant inhibition in four different in vivo solid tumor model and in organ infiltration of acute myeloid leukemia model [70]. Other research has indicated that b-AP15-induced apoptosis depends on the activation of AP-1, with enhancing of oxidative stress and rapid activation of Jun-N-terminal kinase 1/2 (JNK) signaling [71]. The strong antitumor activity of b-AP15 was reported to be due to its intensive enrichment in cells and the resulting rapid commitment to cell death [72]. It could also induce an excessive accumulation of polyubiquitinated proteins and decrease of mitochondrial oxidative phosphorylation thus leading to strong proteotoxic stress and mitochondrial damage [73]. Another study demonstrated that targeting of USP14 and UCHL5 by b-AP15 resulted in a build-up of ubiquitinated proteins and the activation of the endoplasmic reticulum stress response [74].

VLX1570, a derivative of b-AP15, was identified to inhibit proteasome DUBs (including USP14 and UCHL5) activity in vitro in a manner consistent with competitive inhibition [75]. And VLX1570 showed marked inhibition in vivo xenograft mouse model of Ewing sarcoma [76]. Moreover, treatment with VLX1570 induced the accumulation of proteasome-bound high molecular weight polyubiquitin conjugates and an apoptotic response, as well as extended survival in xenograft in multiple myeloma [77]. Paulus et al. found that targeting USP14 and UCHL5 with VLX1570 could be conducive to ibrutinib- or bortezomib-resistant Waldenstrom macroglobulinemia tumor, with downregulation of BCR-associated elements BTK, MYD88, NFATC, NF-κB and CXCR4 [78].

WP1130, a partly selective DUB inhibitor, exhibits inhibitory activity against DUBs including USP14. USP14 inhibition by WP1130 results in downregulation of antiapoptotic and upregulation of proapoptotic proteins [79]. In addition, treatment of USP14 inhibitor WP1130 led to the unfolded protein response and blocked viral infections [80].

In 2010, Lee et al. firstly described IU1 as a selective small-molecule inhibitor of USP14 [27]. In 2012, Nag et al. found that IU1 suppressed replication of several flaviviruses [81]. It was reported that IU1 could significantly alleviate ventilator-induced rat lung injury by decreasing TNF-α, IL-1β, IL-6 and IL-8 levels and increased IκB expression [82]. In addition, Kiprowska et al. found that in a rat cerebral cortical neuron, IU1 reduced the accumulation of Ub-proteins induced by prostaglandin J2 (PGJ2) and triggered calpain-mediated cleavage of Tau, caspase 3 and spectrin, but failed to enhance proteasomal degradation of Ub-proteins or Tau in neurons [83].

Many other compounds also show inhibitory activity against USP14. In a recent study, platinum pyrithione (PtPT) was detected to inhibit USP14 activity and have selective cytotoxicity to multiple cancer cells without damaging DNA [84]. In 2017, Boselli et al. reported compound that IU1-47, a variant of IU1, is a more effective inhibitor of USP14 than IU1 [85]. Besides, Palmer et al. [86] and Wang et al. [87] also reported IU1 derivatives showed inhibitory activity for USP14, and some of these inhibitors (1D18, 1B10 and IU1-248) were more potent than IU1.

In vivo, miR-4728-3p was identified to promote cancer cells apoptosis via inhibiting USP14 expression in lung cancer [40]. Likewise, it was confirmed that USP14 was capable of being targeted by miR-4782-3p in hepatocellular carcinoma cells [88]. Meanwhile, zinc pyrithione found by Zhao et al. [89] and nickel pyrithione by Lan et al. [90] inhibited the enzymatic activities of USP14 and UCHL5, but not the proteolytic activities of 20S proteasomes.

Moreover, some of these compounds showed potential anti-cancer drug resistance. For example, b-AP15 could decrease the viability bortezomib-resistant in multiple myeloma cells, therefore overcoming bortezomib resistance [19]; VLX1570 was able to induce tumor-specific apoptosis in bortezomib- or ibrutinib-resistant Waldenstrom macroglobulinemia tumor cells [78]; Nickel pyrithione could overcome imatinib resistance by triggering excessive apoptosis in chronic myeloid leukemia cells [90].

6. Conclusions and future remarks

USP14, a deubiquitination enzyme located on 26S proteasomes, is responsible for cleaving ubiquitin moieties from ubiquitin-fused precursors and ubiquitinylated proteins. The role of USP14 in cancer progression is currently being explored. Recently, a series of breakthroughs have been made in further clarifying the role of USP14 in cell proliferation, migration and autophagy in different types of cancers. More importantly, drugs design targeting USP14 in oncotherapy have emerged and shown efficient anti-tumor effects. Therefore, novel USP14 inhibitors presents potential clinical uses for cancer treatment. Further investigation on the molecular signaling pathway of USP14 can offer new insights into its antitumor mechanisms. In the future, the manner of USP14's regulation for the ubiquitin chain of substrate proteins may be a hotspot in cancer research. The development of clinical drugs for USP14 and the combination of drugs with other drugs are also valuable research directions.

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