

# Effect of deubiquitinases in head and neck squamous cell carcinoma (Review)

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**Abstract.** HNSCC includes nasopharyngeal, laryngeal and oral cancers, and its pathogenesis is influenced by various factors. As an essential part of the ubiquitin (Ub)-proteasome system (UPS), deubiquitinating enzymes (DUBs) maintain the homeostasis of Ub molecules and influence the physiological functions of cells and disease processes by removing ubiquitinated proteins. Accumulating evidence has confirmed that the aberrant expression of DUBs is involved in cell proliferation, metastasis, and apoptosis during the development of HNSCC, with some acting as oncogenes and others as tumor-suppressor genes. In this review, the DUBs implicated in HNSCC were summarized and the mechanisms underlying abnormal DUBs expression in signaling pathways were discussed. In addition, given the important role of DUBs in tumorigenesis, recent studies were reviewed and agonists and inhibitors of DUBs were summarized to identify more effective therapeutic strategies.

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## 1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer type worldwide with a consistently increasing incidence (1). HNSCC includes nasopharyngeal, laryngeal and oral cancers (2). HNSCC pathogenesis is influenced by various factors, such as viral infection, cigarette smoking, alcohol consumption, environmental factors and genetic factors (2). The treatment of HNSCC involves a variety

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**Abbreviations:** HNSCC, head and neck squamous cell carcinoma; Ub, ubiquitin; UPS, ubiquitin-proteasome system; E1s, ubiquitin-activating enzymes; E2s, ubiquitin-conjugating enzymes; E3s, ubiquitin ligases; DUBs, deubiquitinating enzymes; ATP, adenosine triphosphate; USPs, ubiquitin-specific proteases; UCHs, ubiquitin carboxy-terminal hydrolases; OTUs, ovarian tumor proteases; MJDs, machado-Joseph disease protein domain proteases; JAMMs, JAMM/MPN domain-associated metallopeptidases; MINDYs, monocyte chemotactic protein-induced proteases family; Mdm2, mouse double minute 2; ATXN3, ataxin-3; JOSD, Josephin domain containing; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, MAPK kinase; ERK, extracellular signal-regulated kinase; HIF, hypoxia-inducible factor; CYLD, lysine 63 deubiquitinase; FBXW7, F-box and WD repeat domain containing 7; HPV, human papillomavirus; TRAF, tumor necrosis factor receptor-associated factor; LSCC, laryngeal squamous cell

carcinoma; NEMO, NF- $\kappa$ B essential modifier; UNP, ubiquitous nuclear protein; RIP1, receptor-interacting protein 1; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; RTKs, receptor tyrosine kinases; OSCC, oral squamous cell carcinoma; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PDK1, 3-phosphoinositide-dependent protein kinase 1; AKT, protein kinase B; PTEN, phosphatase and tensin homolog; OTUD3, OTU domain-containing protein 3; SMAD, SMA and MAD-related protein; EMT, epithelial-mesenchymal transition; PHD, prolyl hydroxylase; VHL, von Hippel-Lindau; APC, adenomatous polyposis coli; CK1a, casein kinase 1a; GSK3, glycogen synthase kinase-3; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; MST, Mammalian sterile 20-like kinase; EZH2, enhancer of zeste homolog 2; YAP, yes-associated protein; TAZ, PDZ-binding motif; TEAD, TEA domain transcription factor; DVL, disheveled segment polarity protein; GPCR, G protein-coupled receptors; MST, macrophage stimulating; HSF1, heat shock transcription factor 1; PD-1, programmed death-1; LMP1, latent membrane protein 1; DUBTAC, deubiquitinase chimeras; CFTR, cystic fibrosis transmembrane conductance regulator

**Key words:** head and neck squamous cell carcinoma, deubiquitinating enzymes, ubiquitin-proteasome system, signaling pathway, targeted therapy

of approaches, including surgery, radiotherapy, chemotherapy and immunotherapy. Despite multiple therapeutic approaches, due to the insidious and highly invasive nature of HNSCC, more than half of patients have a poor prognosis and experience local recurrence or distal metastasis of the tumor, and patients continue to have poor survival and quality of life (3-5). Therefore, further research is needed to explore more efficient and tolerable targeted therapies to improve the clinical prognosis of patients with HNSCC.

The ubiquitin (Ub)-proteasome system (UPS) is an important *in vivo* multicomponent system that is involved in cellular processes related to protein homeostasis and quality control (6,7). Mutations or aberrant expression of the UPS are frequently observed in various malignant tumors, including HNSCC. The UPS is a multistep process that involves several different proteins, including Ub, ub-activating enzymes (E1s), ub-conjugating enzymes (E2s), ub ligases (E3s), proteasomes and deubiquitinating enzymes (DUBs) (8-10). In the UPS pathway, the E1-E2-E3 catalytic cascade modifies the substrate and promotes its degradation. In brief, E1s utilize adenosine triphosphate (ATP) hydrolysis to activate and recruit Ub molecules. Activated Ub binds to E2 by forming a thioester bond and interacts with a specific Ub ligase, E3. Finally, it covalently binds to the target protein via E3. This complex is recognized and degraded, thereby regulating steady-state protein (9,11-13). In addition, the seven acceptor lysines (K6, K11, K27, K29, K33, K48 and K63) of the Ub molecule can participate in sequential conjugation, resulting in various Ub chain links, ultimately determining the various fates and activities of the target proteins. K63, K6, K27 and K33 are involved in numerous key biological processes, including signal transduction, DNA damage and mitochondrial homeostasis (10). K48, K11 and K29 primarily participate in substrate degradation via the 26s proteasome pathway (14,15) (Fig. 1).

Ubiquitination is a highly reversible, dynamic process. DUBs can remove Ub molecules from proteins, thus maintaining the balance of protein functions (11,16,17). So far, ~100 different deubiquitinating enzymes have been identified in humans, and depending on their structure, they can be classified into six families: ubiquitin-specific proteases (USPs), ubiquitin carboxy-terminal hydrolases (UCHs), ovarian tumor proteases (OTUs), Machado-Joseph disease protein domain proteases (MJDs), JAMM/MPN domain-associated metalloproteinases (JAMMs) and the monocyte chemotactic protein-induced proteases family (MINDYs) (18-20). Among them, the USP family, which consists of finger, palm and thumb domains, is the most extensively studied family of small-molecule inhibitors (21). The UCH family is a group of small molecular-weight cysteine proteases that promote ubiquitin recycling (16). Similar to the UCH family, the OTU family has three subgroups: OTU, OTUB and A20-like OTU, each having a distinct specificity for certain types of ubiquitin chains. There are four MJD family members: ataxin-3 (ATXN3), ATXN3L, Josephin domain containing 1 (JOSD1) and JOSD2. One of the most intensively studied enzymes is ATXN3, a cysteine protease (22,23). The JAMM/MPN family of metalloproteinases can bind ubiquitinated proteins to Ub molecules (24,25). The MINDY family remains largely elusive and specializes in cutting long Ub chains, such as the K48 Ub chain (26).

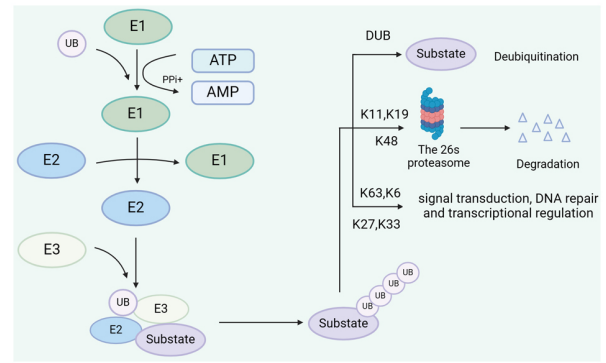


Figure 1. Ubiquitination processes. This system includes Ub, E1s, E2s, E3s, proteasome and DUBs. E1s utilize ATP hydrolysis to activate and recruit Ub molecules. Activated Ub binds to E2 by forming a thioester bond and interacts with E3. Finally, it covalently binds to the target protein mediated by E3. In addition, the ubiquitin linkage type determines the different fates and functions of target proteins: K63, K6, K27 and K33 are involved in numerous key biological processes, including signal transduction, DNA damage and mitochondrial homeostasis, while K48, K11 and K29 primarily participate in substrate degradation by the 26s proteasome pathway. Ub, ubiquitin; ATP, adenosine triphosphate; DUBs, deubiquitinating enzymes.

Recent advances in clinical research, targeted therapy and immunotherapy have shown promising efficacy in HNSCC. In addition, the widespread use of genetic testing has led to the discovery of an increasing number of affected genes in HNSCC, providing guidelines for the selection of targeted drugs (27). Of note, mutations or dysregulation in ubiquitination modifications can trigger a wide range of serious human diseases, including cancer. The present review focused on the different signaling dysregulations associated with DUBs in HNSCC to identify potential therapeutic targets and improve the therapeutic efficacy of HNSCC.

## 2. DUBs in signaling pathways associated with HNSCC

DUBs have been reported to act as key regulators of the development and progression of HNSCC. In addition, DUBs regulate various HNSCC-related signaling pathways, including the p53 signaling pathway, NF- $\kappa$ B signaling pathway, rat sarcoma (RAS)/rapidly accelerated fibrosarcoma (RAF)/MAPK kinase (MEK)/extracellular signal-regulated kinase (ERK), PI3K signaling pathway, TGF- $\beta$  signaling pathway, hypoxia-inducible factor (HIF)-1 $\alpha$ , Wnt/ $\beta$ -catenin, MYC signaling pathway and Hippo pathways.

In this chapter, the DUBs implicated in HNSCC were summarized and the mechanisms underlying abnormal DUBs expression in signaling pathways were discussed. For instance, USP7 can promote cancer development by downregulating p53 levels through deubiquitination of mouse double minute 2 (MDM2); lysine 63 deubiquitinase (CYLD), which is frequently mutated in nasopharyngeal carcinoma, inhibits cell invasion and metastasis by interfering with the NF- $\kappa$ B signaling pathway; USP28 is an oncogenic factor that deubiquitinates F-box and WD repeat domain containing 7 (FBXW7), thereby enhancing the stability of RAF family members and inhibiting activation of the MEEK pathway. In addition, recent studies were reviewed and agonists and inhibitors of DUBs

Table I. HNSCC-associated DUBs.

Pathway/types	DUB	Substrate in HNSCC	Deubiquitination-induced change	Potential role in HNSCC	(Refs.)
p53 signaling pathway - USPs	USP7	MDM2	Promotes p53 signaling pathway degradation	Oncogene	(42)
NF-κB signaling pathway - USPs	CYLD	NEMO	Not reported	Tumor suppressor	(54,55)
NF-κB signaling pathway - USPs	USP4	RIP	Suppression of NF-κB signaling pathway	Tumor suppressor	(58)
RAS/RAF/MEK/ERK pathway - USPs	USP28	FBXW7	Suppression of MEEK pathway	Tumor suppressor	(71)
PI3K signaling pathway - USPs	USP13	PTEN	Stabilise PTEN	Tumor suppressor	(83)
PI3K signaling pathway - OTUs	OTUD3	PTEN	Stabilise PTEN	Tumor suppressor	(89,90)
PI3K signaling pathway - USPs	USP1	AKT	Stabilise AKT	Tumor suppressor	(99)
TGF-β signaling pathway - USPs	CYLD	TGF-βRI	Activates the TGF-β signaling pathway	Oncogene	(108)
HIF-1α pathway - UCHs	UCHL1	VHL	Activates the HIF-1α pathway	Oncogene	(120)
Wnt/β-catenin pathway - USPs	USP7	EZH2	Suppression of Wnt/β-catenin pathway	Tumor suppressor	(131)
MYC signaling pathway - USPs	USP22	Not reported	Not reported	Oncogene	(137)
Hippo pathway - UCHs	UCHL3	YAP	Stabilizes and maintains YAP	Oncogene	(152)
Others - USPs	USP14	HSF1	Protein stability	Oncogene	(153)
Others - USPs	USP9X	PD-L1	Protein stability	Oncogene	(173)

HNSCC, head and neck squamous cell carcinoma; DUBs, deubiquitinating enzymes; USPs, ubiquitin-specific proteases; MDM2, mouse double minute 2; CYLD, lysine 63 deubiquitinase; NEMO, NF-κB essential modifier; RIP, receptor-interacting protein; FBXW7, F-box and WD repeat domain containing 7; PTEN, phosphatase and tensin homolog; OTUD3, OTU domain-containing protein 3; UCHL1, ubiquitin carboxyl terminal hydrolase L1; TGF-β, transforming growth factor-β; YAP, yes-associated protein; HSF1, heat shock transcription factor 1.

were summarized to identify more effective therapeutic strategies (Table I, Figs. 2-4).

**p53 Pathway.** p53 has a critical role in the cell cycle and is considered an important tumor suppressor. When stimulated by cellular stress or DNA damage, a sequence of phosphorylation events activates p53 (28). Notably, p53 is frequently mutated and aberrant stability of p53 has been observed in HNSCC (29,30). Emerging evidence has shown that various E3 ligases mediate the ubiquitination and stability of p53 (31). For instance, the E3 ligase Mdm2 can maintain p53 at normal levels *in vivo* by accelerating its degradation of p53 under normal conditions (32). Furthermore, p53 is readjusted by deubiquitination via deubiquitinating enzymes that can eliminate Ub molecules from p53. p53 is important in genome stabilization and is the most common mutation gene in human papillomavirus (HPV)-negative patients with HNSCC (33). Compared to patients with normal p53 expression, patients with mutations have an increased oncogenic potential, poor sensitivity to radiotherapy and an increased rate of tumor recurrence, eventually leading to reduced survival (34). A summary of the different DUBs involved in the regulation of

the p53 signaling pathway may provide new insights for understanding the occurrence and progression of HNSCC (35,36).

**USP7.** USP7 was first identified to interact with herpes simplex viruses; thus, it is also known as a herpesvirus-associated Ub-specific protease (37). Functionally, USP7 is considered an oncogenic protein that removes Ub and prevents substrate degradation. Studies have found that USP7 is associated with a wide range of pathologies, including neurological lesions, inflammatory responses and tumors (38). USP7 comprises three structural domains: The tumor necrosis factor receptor-associated factor (TRAF) domain, a highly conserved USP domain, and five ubiquitin-like domains 1-5 (39,40). It is known that the p53 protein can be degraded by MDM2, and the TRAF-like domain of USP7 can mediate the deubiquitination of MDM2, increasing intracellular levels of MDM2, which in turn downregulates p53 (41). Therefore, inhibition of USP7 activity can stabilize p53 levels, thus generating anti-apoptotic functions (42). Recently, Niu *et al* (43) found that high expression of USP7 reduces radiosensitivity in laryngeal squamous cell carcinoma (LSCC) with p53 mutations, and clinical application of USP7 inhibitors in the future may improve the effects of radiotherapy for patients. Therefore, to

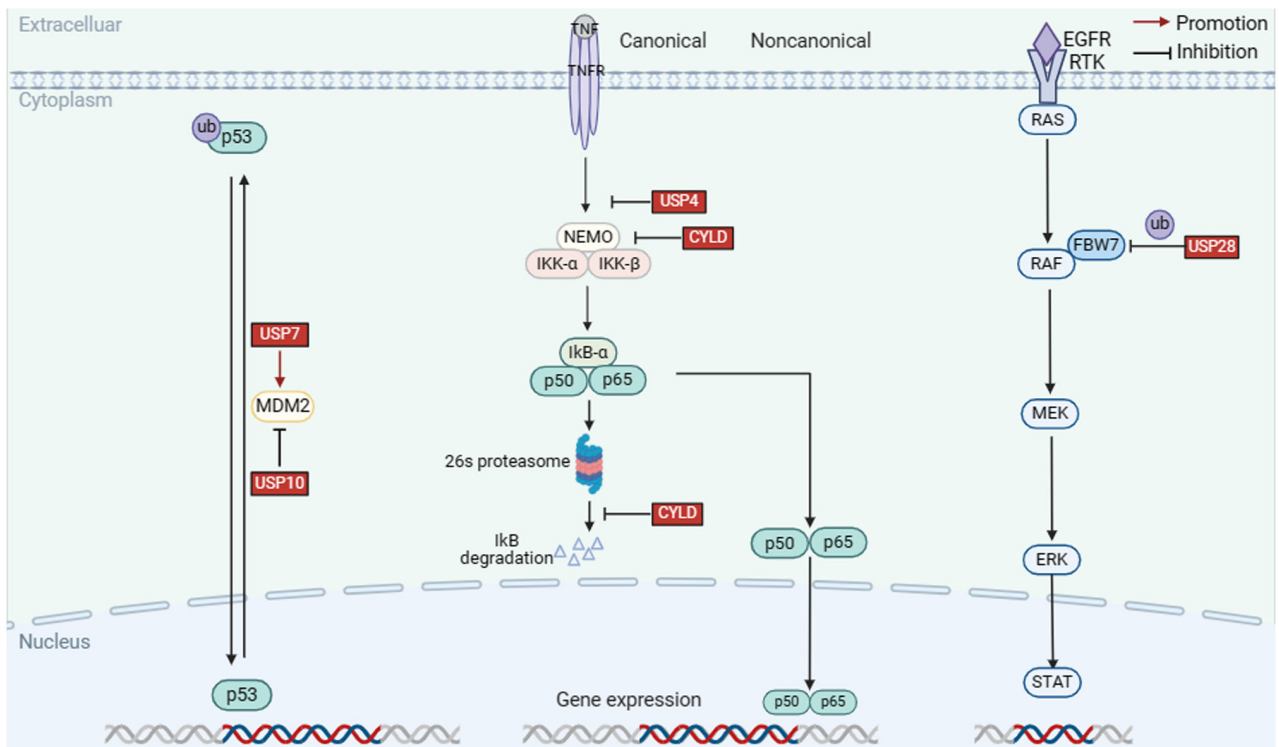


Figure 2. Roles of DUBs in the p53 pathway, NF- $\kappa$ B signaling pathway and RAS/RAF/MEK/ERK pathway in HNSCC. p53 signaling pathway: When stimulated by cellular stress or DNA damage, a sequence of phosphorylation events activates p53. USP7 is a key regulator of the p53 pathway, which deubiquitinates MDM2, increasing the intracellular level of MDM2, which in turn downregulates p53. NF- $\kappa$ B signaling pathway: In the canonical pathway, the IKK complex is activated and induces phosphorylation of IKK- $\beta$ ; subsequently, IKK- $\beta$  phosphorylates I $\kappa$ B- $\alpha$ , causing its ubiquitination and degradation by the 26S proteasome. Next, the p65/p50 dimer is released and enters the nucleus to turn on the downstream target genes. Mechanistically, CYLD can interfere with the NF- $\kappa$ B signaling pathway through deubiquitination of TRAF2 or Bcl-3, while USP4 represses NF- $\kappa$ B activation by interacting and deubiquitinating with RIP1. RAS/RAF/MEK/ERK pathway: When extracellular signals stimulate the cell, RAS recruits the RAF kinase for activation, and then RAF continues to activate downstream MEK and ERK, and eventually delivers cell proliferation and differentiation signals to the nucleus. USP28 deubiquitinates FBW7, and increases ubiquitination and degradation of B-RAF, thereby enhancing the stability of RAF family members. DUBs, deubiquitinating enzymes; NF- $\kappa$ B, nuclear factor  $\kappa$ B; HNSCC, head and neck squamous cell carcinoma; UPS, ubiquitin-proteasome system; USPs, ubiquitin-specific proteases; Mdm2, mouse double minute 2; NEMO, NF- $\kappa$ B essential modifier; CYLD, lysine 63 deubiquitinase; TRAF2, TNF receptor-associated factor 2; RIP1, receptor-interacting protein 1; RAS, Rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; EGFR, epidermal growth factor receptor; RTKs, receptor tyrosine kinases; FBW7, F-box and WD repeat domain containing 7.

further explore the expression of USP7 in HNSCC, The Cancer Genome Atlas (<https://portal.gdc.cancer.gov/>) database was analyzed, indicating that the expression level of USP7 mRNA in HNSCC tissues was higher than that in normal tissues (Table SI). Furthermore, an analysis of the Clinical Proteomic Tumor Analysis Consortium (<https://proteomics.cancer.gov/>) database suggested that USP7 protein expression was significantly upregulated in HNSCC (Table SII).

**NF- $\kappa$ B signaling pathway.** NF- $\kappa$ B is a nuclear transcription factor, and dysregulation of NF- $\kappa$ B activity can cause inflammation-related diseases and cancers (44). In the canonical pathway, the IKK complex containing IKK- $\alpha$ , IKK- $\beta$  and NF- $\kappa$ B essential modifier (NEMO) is activated and induces the phosphorylation of IKK- $\beta$ , which then phosphorylates I $\kappa$ B- $\alpha$ , causing ubiquitination and degradation by the 26S proteasome (45). Next, the p65/p50 dimer is released and enters the nucleus to activate downstream target genes (45,46). Accumulating evidence has demonstrated that the NF- $\kappa$ B signaling pathway is commonly activated during the occurrence and progression of HNSCC to regulate cell proliferation, invasion, angiogenesis and metastasis (47,48). It has been reported that DUBs can regulate the activation of the NF- $\kappa$ B

pathway by removing polyubiquitin chains, suggesting that it is a potential therapeutic target (49).

**CYLD.** As a putative tumor suppressor gene, CYLD encodes an evolutionarily conserved protein of ~120 kDa (956aa) (50). CYLD contains a deubiquitinating enzyme catalytic structural domain and three CAP-Gly structural domains (51). TRAF2 is a component of a complex that can activate NEMO; mechanistically, CYLD can negatively regulate TRAF2-mediated IKK activation by removing the k63-polyubiquitin chain on TRAF2, thereby interfering with the NF- $\kappa$ B signaling pathway and inhibiting cell growth (52). Bcl-3 is an atypical member of the I $\kappa$ B protein family and a regulator of NF- $\kappa$ B, which activates the NF- $\kappa$ B pathway through the deubiquitination of Bcl-3 (53). CYLD mutations have also been reported in patients with HNSCC; CYLD is one of the most mutated genes in nasopharyngeal carcinoma, and according to functional assays, CYLD negatively regulates NF- $\kappa$ B by preventing nuclear translocation of p65, thereby inhibiting cell invasion and metastasis, enhancing the surveillance of patients with HNSCC (54,55).

**USP4.** USP4, a ubiquitous nuclear protein (UNP), contains a catalytic domain and a non-catalytic domain, capable of removing monoubiquitinated and polyubiquitinated

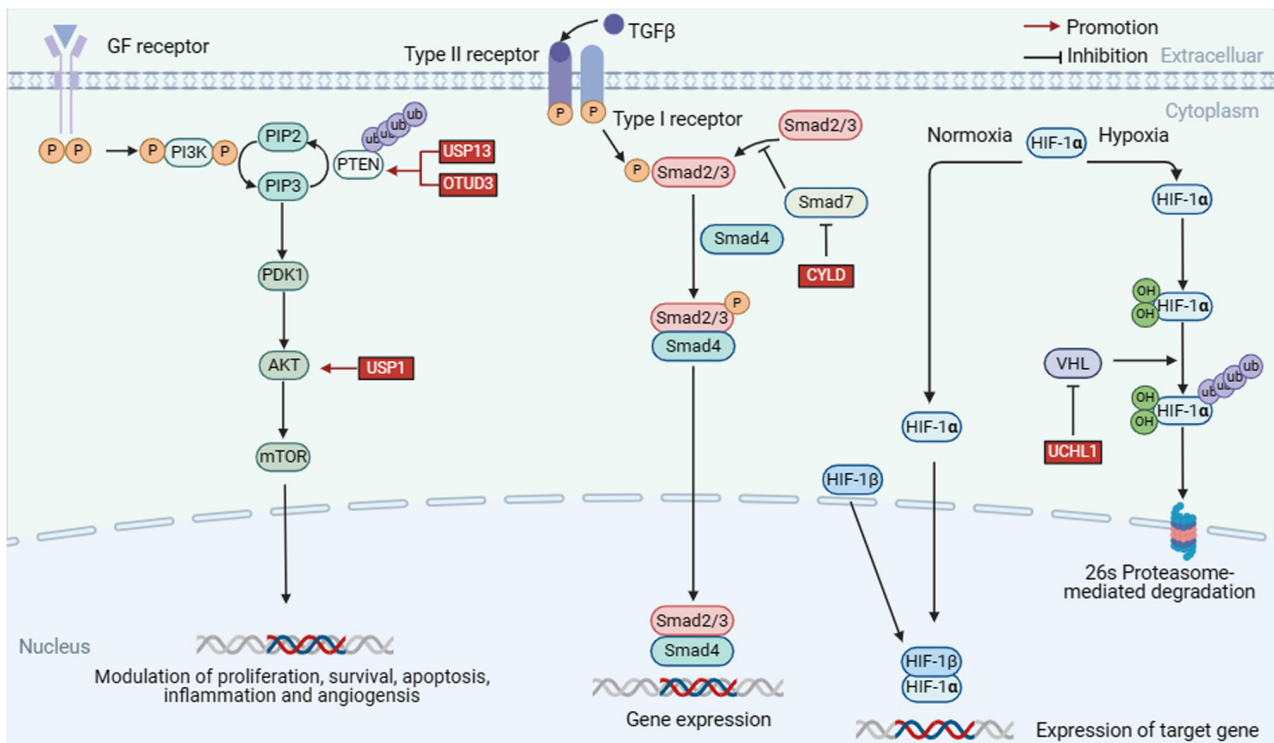


Figure 3. Roles of DUBs in the PI3K, TGF- $\beta$  and HIF-1 $\alpha$  signaling pathway in HNSCC. PI3K signaling pathway: Activated PI3K catalyzes PIP2 to generate PIP3, which acts as a second messenger and recruits PDK1 and AKT proteins to the plasma membrane. Subsequently, PDK1 phosphorylates and activates AKT proteins, activating downstream pathways. USP13 and OTUD3 can deubiquitinate PTEN, thereby increasing PTEN protein stability and inhibiting carcinogenic PI3K/AKT signaling. USP1 is involved in the PI3K/AKT signaling pathway by removing K63-linked polyubiquitin chains on AKT. TGF- $\beta$  signaling pathway: Activated TGF- $\beta$  ligand interacts with TGF- $\beta$ R1 and TGF- $\beta$ R2, forming a tetrameric complex. Subsequently, TGF- $\beta$ R2 phosphorylates TGF- $\beta$ R1. SMAD 2/3 may be phosphorylated by activated TGF- $\beta$ R1 and form heteromeric complexes with SMAD4. Finally, SMAD 2/3-SMAD4 complexes are transported into the nucleus and regulate gene expression. CYLD stabilizes TGF- $\beta$ R1 by removing the K63-linked polyubiquitin chain on Smad7 and consequently promotes TGF- $\beta$  signaling. HIF-1 $\alpha$  pathway: Under aerobic conditions, PHD hydroxylates HIF-1 $\alpha$ . Next, VHL mediates HIF-1 $\alpha$  to be rapidly and persistently degraded by the proteasome pathway. Under hypoxia, the activity of PHD and VHL is inhibited by low oxygen, leading to stabilization and activation of HIF-1 $\alpha$ . UCHL1 has been reported to inhibit the VHL-mediated ubiquitination of HIF-1 $\alpha$ . PI3K, phosphoinositide 3-kinase; CYLD, lysine 63 deubiquitinase; TGF- $\beta$ , transforming growth factor- $\beta$ ; HIF-1 $\alpha$ , hypoxia-inducible factor-1 $\alpha$ ; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PDK1, 3-phosphoinositide-dependent protein kinase 1; AKT, protein kinase B; USPs, ubiquitin-specific proteases; OTUD3, OTU domain-containing protein 3; PTEN, phosphatase and tensin homolog; SMAD, SMA and MAD-related; PHD, prolyl hydroxylase; VHL, von Hippel-Lindau; UCHs, ubiquitin carboxy-terminal hydrolases.

chains (56). USP4 is involved in various pathological conditions, including hypertrophic cardiomyopathy and malignancy. USP4 is abnormally expressed in brain, breast and lung cancer (56,57). USP4 has also been reported to play a tumor-suppressive role in HNSCC. Hou *et al* (58) found that USP4 expression levels are significantly higher in HNSCC tissues in normal tissues. Receptor-interacting protein 1 (RIP1) is an upstream signaling molecule of NF- $\kappa$ B signaling that is essential for the regulation of apoptosis. Further research has demonstrated that USP4 suppresses tumor growth by interacting with RIP1, deubiquitinating K63-linked RIP1 and inhibiting NF- $\kappa$ B activation, resulting in tumor suppressor effects (58).

**RAS/RAF/MEK/ERK pathway.** The RAS/RAF/MEK/ERK pathway is one of the most important components of all MAPK signal transduction pathways, which are essential for the regulation of basic intercellular and intracellular functions, such as growth, survival and differentiation, thereby promoting the growth and metastasis of tumor cells (59). Activation of the MAPK signaling pathway is present in nearly one-fifth of HNSCC cases, leading to the expression of downstream genes,

including Bcl-2, HIF-1 $\alpha$  and vascular endothelial growth factor (VEGF), which affect the invasive, hypoxic, angiogenic and inflammatory processes in HNSCC (60-62).

Numerous stimulating factors, such as epidermal growth factor (EGF), receptor tyrosine kinases, TNF and Src family members, can activate an upstream activating protein known as RAS, subsequently triggers many downstream proteins and recruits the RAF kinase to the plasma membrane for activation (63,64). Activated RAF then activates downstream MEK and MAPK/ERK, eventually delivering cell proliferation and differentiation signals to the nucleus by regulating the activity of various transcriptional regulators that contribute to gene expression (60,64).

Aberrant activation of the RAS/RAF/MEK/ERK signaling pathway was reported to be associated with the development and progression of HNSCC (60).

**USP28.** USP28 is a functional protein belonging to the USP family that plays a key role in various biological processes, including DNA damage repair, transcription factor regulation and carcinogenesis (65,66). It's also found that USP28, which is located on chromosome 11q23, is frequently mutated in HNSCC (67). FBXW7 is considered a tumor suppressor,

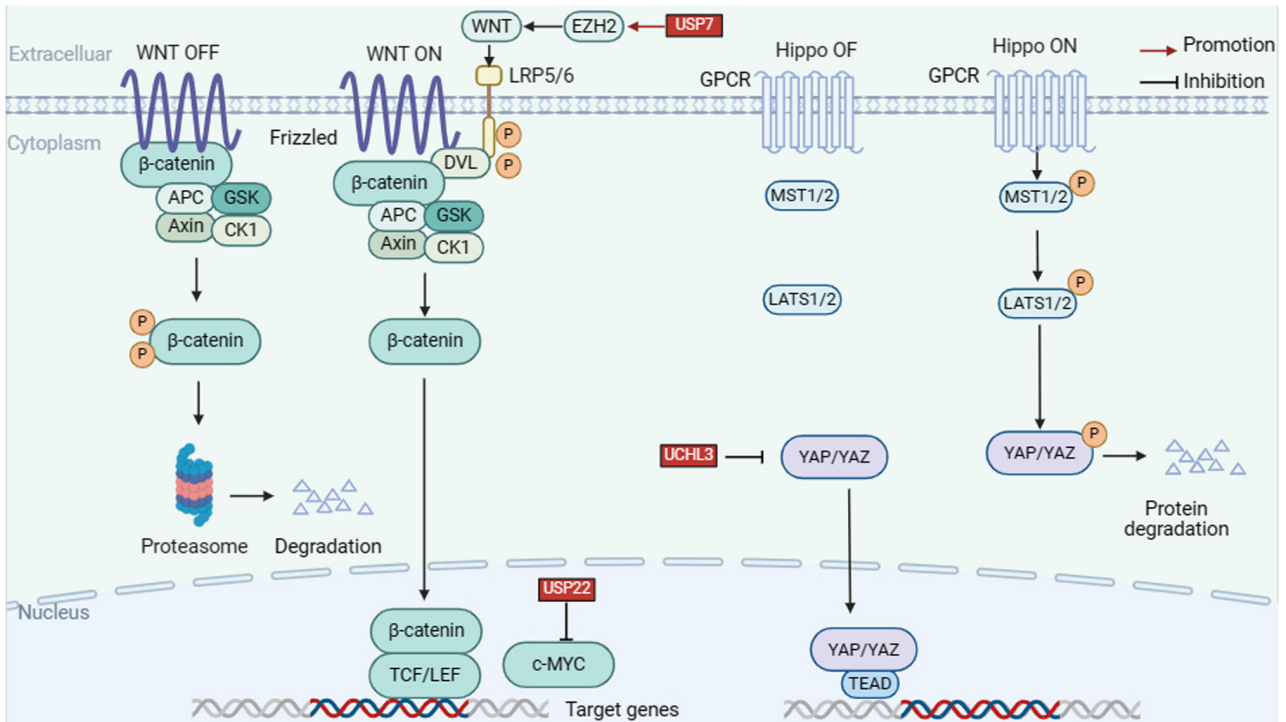


Figure 4. Roles of DUBs in Wnt/ $\beta$ -catenin pathway, MYC signaling pathway and Hippo pathway in HNSCC. Wnt/ $\beta$ -catenin pathway: When there is no Wnt signal present in the cell, a destructive complex that consists of APC protein, Axin, CK1a, GSK3 and  $\beta$ -catenin degrades cytoplasmic  $\beta$ -catenin. After the formation of the complex,  $\beta$ -catenin begins to be phosphorylated sequentially and undergoes UPS-mediated degradation. Wnt signaling is activated and the Wnt ligand forms complexes by binding to Frizzled receptor and Lrp5/6. After complex formation, scaffold proteins are recruited to the receptor, which is phosphorylated and inhibits degradation of  $\beta$ -linker proteins. This allows  $\beta$ -catenin proteins to translocate into the nucleus, where they bind to TCF/LEF transcription factors, activating the transcription of Wnt target genes. USP7 is able to inhibit the expression of the Wnt/ $\beta$ -catenin pathway; however, the underlying mechanism remains elusive. MYC signaling pathway: MYC is activated by the nuclear translocation of  $\beta$ -catenin, and maintains intracellular homeostasis and cell proliferation. USP22 is a positive regulator of the MYC signaling pathway but the molecular mechanism remains to be elucidated. Hippo pathway: Physiologically, the Hippo pathway is normally active and the LATS1/2 kinases are phosphorylated and activated by MST1 and MST2. Subsequently, LATS1/2 kinases phosphorylate YAP and TAZ, ultimately leading to nuclear exclusion of YAP/TAZ. YAP and TAZ translocate to the nucleus when the core Hippo kinases are inactive; subsequently, they bind to TEAD family proteins to promote cell growth and proliferation or interact with other transcription factors or signaling molecules. UCHL3 is a new YAP-deubiquitinating enzyme with the ability to regulate YAP deubiquitination and stabilization. APC, adenomatous polyposis coli; CK1a, casein kinase 1a; GSK3, glycogen synthase kinase-3; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; MST, Mammalian sterile 20-like kinase; EZH2, enhancer of zeste homolog 2; YAP, Yes-associated protein; TAZ, PDZ-binding motif; TEAD, TEA domain transcription factor; UCHs, ubiquitin carboxy-terminal hydrolases; DVL, disheveled segment polarity protein; GPCR, G protein-coupled receptors.

which is a component of the Ub ligase complex and can regulate the protein stability of B-RAF, a member of the RAF family (68). Certain studies have suggested that FBXW7 is anomalously expressed in various cancers, such as oral squamous cell carcinoma (OSCC) and esophageal squamous cell carcinoma (69,70). USP28 deubiquitinates and stabilizes FBW7, allowing the WD40 repeat sequence in FBW7 to bind and degrade substrates containing Cdc4 phosphorylation motifs, and it was found that the Cdc4 phosphorylation structural domains are widely present in human RAF subtypes. In conclusion, USP28 can destabilize RAF family members by indirectly increasing ubiquitination and degradation of B-RAF via FBW7 (71). Notably, RAF is an important target in the MAPK signaling pathway, and several inhibitors have been advanced to improve patient survival (72).

**PI3K/AKT signaling pathway.** Aberrant activation of the PI3K/AKT signaling pathway commonly occurs in cancer. As a downstream molecule of PI3K, AKT is a major effector of PI3K in cancers (73). Activated PI3K catalyzes phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP<sub>3</sub>), which serves as a

second messenger and recruits 3-phosphoinositide-dependent protein kinase 1 (PDK1) and AKT to the plasma membrane. Subsequently, PDK1 phosphorylates and activates AKT, which further activates the downstream pathways that regulate metastasis, metabolism and cell survival (74,75).

The PI3K/AKT signaling pathway is upregulated in >90% of HNSCC and is more evident in HPV-positive patients (76). Studies have shown that upregulation of the PI3K/AKT signaling pathway enhances resistance to radiotherapy and drugs by modulating cellular distribution during the cell cycle (77). Therefore, the development of selective inhibitors offers potential therapeutic opportunities for patients.

As a tumor suppressor gene, phosphatase and tensin homolog (PTEN) is frequently lost or mutated in tumors, reducing PI3K activity by converting PIP<sub>3</sub> back to PIP<sub>2</sub> (78). Loss of PTEN causes consistent activation of the PI3K pathway, leading to tumorigenesis (79,80).

Notably, several deubiquitinating enzymes, including USP13, OTU domain-containing protein 3 (OTUD3) and USP1, can deubiquitinate PTEN in cancer-specific contexts, thereby maintaining PTEN levels and preventing its degradation (81).

**USP13.** Structurally, USP13 consists of 863 amino acids and contains highly conserved zinc finger structural domains and USP catalytic structural domains (82). USP13 is the first PTEN deubiquitinating enzyme discovered, which binds to the phosphatase domain of PTEN and stabilizes PTEN levels through deubiquitination, inhibiting tumor development and glycolysis. Studies have shown that inhibition of PTEN by deletion of USP13 leads to aberrant phosphorylation of AKT, which affects downstream genes associated with cell survival, metabolism and growth (83). Meanwhile, Qu *et al* (84) found that the interaction between USP13 and PTEN ultimately inhibited AKT phosphorylation. The expression of USP13 is frequently reduced in OSCC tissues as indicated by immunohistochemical staining, suggesting that USP13 may act as a tumor suppressive role in OSCC (84-86).

**OTUD3.** OTUD3 is a member of the OTU family that participates in the regulation of multiple physiological processes, and the aberrant expression of OTUD3 triggers tumorigenesis in esophageal cancer, breast cancer and papillary thyroid carcinoma (87,88). Several studies have demonstrated that OTUD3 interacts with PTEN and induces its deubiquitination, increasing PTEN protein stability and inhibiting carcinogenic PI3K/AKT signaling (89). Mechanistically, OTUD3 binds to the PTEN C2 domain, a region that has been demonstrated to play a critical role in PTEN stability control and regulation of cell migration, and preferentially removes the K6, K11, K27 and K48 linkages of PTEN ubiquitination (89,90). Notably, Zhao *et al* (90) discovered that in thyroid carcinoma, OTUD3 deubiquitinates PTEN, thereby increasing PTEN protein stability and inhibiting the activation of PI3K/AKT signaling.

**USP1.** USP1 is a key deubiquitinating enzyme in the USP family. Structurally, it can be divided into a catalytically active C-terminal domain and a regulatory N-terminal domain (91). USP1 is expressed in a wide range of human tissues and participates in the regulation of DNA damage repair, cell cycle regulation, and tumor progression (92-95). Furthermore, the expression and function of USP1 have been reported to be associated with multiple cancers, including breast cancer, lung cancer, hepatocellular carcinoma, and HNSCC (96-98). Xu *et al* (92) found that USP1 is involved in the PI3K/AKT signaling pathway by removing K63-linked polyubiquitin chains from AKT. They used a PI3K inhibitor (S2793) to reverse the effects of USP1 and found that USP1 overexpression activated the PI3K/AKT signaling pathway, causing tumor cell migration and invasion in HNSCC (92,99).

**TGF- $\beta$  signaling pathway.** TGF- $\beta$  is a family of structurally related proteins. TGF- $\beta$  ligands bind to TGF- $\beta$ RII, recruiting and phosphorylating TGF- $\beta$ RI (100,101). SMA and MAD-related family protein (SMAD)2/3 may be phosphorylated by activated TGF- $\beta$ RI and form heteromeric complexes with SMAD4 (102). Finally, SMAD2/3-SMAD4 complexes are transported into the nucleus where they activate multiple downstream signaling pathways and regulate the expression of various genes (102,103). TGF- $\beta$  upregulation may be involved in the recurrence and metastasis of HNSCC (104). Specifically, TGF- $\beta$  upregulation regulates the expression of various genes, including the process of inducing epithelial-mesenchymal transition (EMT) and the

regulation of VEGF, which drives cancer cell migration and angiogenesis (104,105).

SMAD7 is a key negative regulator of TGF- $\beta$  signaling, which bind to TGF- $\beta$ RI and competitively inhibit the phosphorylation of SMAD2/3, blocking the interaction between SMAD2/3 and the receptor complex, thereby inhibiting the downstream TGF- $\beta$  signaling pathway (106). In certain instances, E3 ubiquitin ligases were observed to repress TGF- $\beta$  signaling by interacting with SMAD7. This section focuses on the role of DUBs, which counteract the activity of E3 ubiquitin ligases and maintain TGF- $\beta$  signaling pathways.

**CYLD.** Multiple studies have shown that CYLD plays an important role in the NF- $\kappa$ B signaling pathway, and it has also been proven that CYLD plays a role in regulating the TGF- $\beta$  signaling pathway (107). Decreased CYLD expression promotes the invasion of OSCC cells. A study found that the loss of CYLD stabilized TGF- $\beta$ RI by removing the k63-linked polyubiquitin chain on SMAD7, and consequently promoted TGF- $\beta$  signaling in OSCC cells (108).

**HIF-1 $\alpha$  pathway.** As an oxygen-dependent transcriptional activator, HIF-1 $\alpha$  is widespread in mammalian and human cells, and is composed of an  $\alpha$  subunit HIF-1 $\alpha$  and a  $\beta$  subunit HIF-1 $\beta$  (109). In addition, experimental data have demonstrated that HIF-1 $\alpha$  is one of the key regulators of >100 genes downstream (110).

Under aerobic conditions, the activity of prolyl hydroxylase (PHD) is regulated by oxygen, leading to hydroxylation of HIF-1 $\alpha$ . Next, von Hippel Lindau (VHL) incorporates the hydroxylated subunit, leading to rapid and sustained degradation of HIF-1 $\alpha$  via the proteasome pathway (111,112). However, under hypoxic conditions, the activities of PHD and VHL are inhibited by low oxygen levels, leading to the stabilization and activation of HIF-1 $\alpha$  (111). Subsequently, it escapes degradation and is transported into the cell nucleus, where it regulates numerous downstream genes implicated in cancer progression (111). It then avoids destruction and enters the cell nucleus, where it upregulates numerous downstream genes implicated in the development of cancer (113). Studies have shown that overexpression of HIF-1 $\alpha$  is associated with poor overall survival in nasopharyngeal, oropharyngeal and oral carcinomas, but no link has been found in laryngeal carcinoma (114).

**UCHL1.** UCHL1 is a DUB enzyme that belongs to the UCHs family (115). It controls diverse cellular processes such as metabolism, protein aggregation and autophagy by deubiquitinating multiple key substrate proteins (116). Furthermore, the expression of UCHL1 has been demonstrated to be dysregulated in several tumor types, including pancreatic, colorectal and breast cancers, where it can enhance cancer invasion and metastasis (117,118). Zhang *et al* (119) found that UCHL1 is highly expressed in HNSCC tissues and contributes to the proliferation and metastasis of HNSCC.

Furthermore, Li *et al* (120) found that cell migration is markedly enhanced by UCHL1 expression. In 3D spheroid culture models, certain malignancy-related factors, including solidity, volume and viable cell number, were considerably increased by the ectopic expression of UCHL1 in an HIF-1 $\alpha$ -dependent manner. By contrast, these malignancy-related factors are downregulated when the HIF-1 $\alpha$

pathway were inhibited and UCHL1-mediated cell invasion and proliferation were eliminated (120,121). As a novel upstream activator of HIF-1 $\alpha$ , UCHL1 inhibits VHL-mediated ubiquitination of HIF-1 $\alpha$ . These findings suggest that, as a deubiquitinating enzyme for HIF-1 $\alpha$ , UCHL1 may be a prognostic indicator and therapeutic target for cancers because it promotes metastases (122).

*Wnt/ $\beta$ -catenin pathway.* The Wnt/ $\beta$ -catenin pathway is a complex network of protein actions. When there is no Wnt signal in the cell, a destructive complex consisting of adenomatous polyposis coli (APC) protein, Axin, casein kinase 1a (CK1a), glycogen synthase kinase-3 and  $\beta$ -catenin can degrade cytoplasmic  $\beta$ -catenin (123). Wnt signaling is activated when Wnt proteins bind to the structural domains of the Frizzled family receptors, which form complexes by binding to the Frizzled receptor and protein 5/6. After complex formation, scaffold proteins are recruited to the receptor, which is phosphorylated and inhibits the degradation of the  $\beta$ -linker proteins. This allows  $\beta$ -catenin proteins to accumulate and translocate into the nucleus, where they bind to TCF/LEF transcription factors, thereby activating the transcription of Wnt target genes and inducing subsequent cellular responses (124,125).

$\beta$ -catenin is an important regulator of Wnt/ $\beta$ -catenin signaling. Yang *et al* (126) observed that the level of  $\beta$ -catenin was positively correlated with the cell invasion potential in HNSCC. Further experiments showed that activation of Wnt/ $\beta$ -catenin signaling not only promotes cell invasion, but also stimulates lymph node metastasis in HNSCC, and these results suggest that blocking the Wnt/ $\beta$ -catenin signaling may be a therapeutic strategy for lymph node metastasis and tumor recurrence in HNSCC (127).

*USP7.* USP7 functions as a tumor suppressor and stabilizes p53. Zheng *et al* (128) discovered the mechanism by which USP7 acts on the substrate EZH2, an interaction between the two was found by immunoprecipitation, and further experiments showed that overexpression of USP7 led to a decrease in ubiquitination of EZH2. EZH2 is able to inhibit multiple Wnt genes, thereby silencing Wnt/ $\beta$ -catenin signaling. Experimental results showed that USP7 overexpression suppressed the expression of several pathway-related genes, including Wnt, promoting cellular EMT and inhibiting cellular senescence and differentiation (128-130). One study suggested that USP7 and EZH2 are upregulated in LSCC tissues, which affects LSCC evolution and serves as an independent prognostic predictor. Thus, USP7 may serve as a novel therapeutic target (131).

*MYC signaling pathway.* It is well known that MYC is a proto-oncogene expressed in various cancers, including HNSCC (132). MYC is an important transcription factor that plays a key role in regulating cellular metabolic processes (133). As a target gene of the Wnt/ $\beta$ -catenin pathway, MYC is activated by the nuclear translocation of  $\beta$ -catenin and maintains intracellular homeostasis and cell proliferation (134). The stability of the MYC protein is primarily regulated by the UPS. For instance, MYC is converted to ubiquitin by SCFFBW7 and several other E3 ubiquitin ligases (135). However, little is known about MYC deubiquitination. The following section focuses on the process of MYC-associated deubiquitination.

*USP22.* USP22 is located on chromosome 17 and is composed of 14 exons. USP22 regulates the transcriptional activation of numerous genes by histone ubiquitination (H2A and H2B) and affects chromatin structures (136). It was found that USP22 positively regulates MYC protein levels and that USP22 promotes cancer progression by targeting k48-linked polyubiquitin chains to deubiquitinate MYC (137). Several studies have shown that USP22 is overexpressed in HNSCC and closely associated with the growth and proliferation of tumor cells (20). For instance, USP22 expression is enhanced in laryngeal carcinoma, contributing to invasion, metastasis and poor prognosis (138).

*Hippo pathway.* The Hippo pathway is a tumor suppressor pathway and dysregulation of its effector Yes-associated protein (YAP) and PDZ-binding motif (TAZ) is an important factor in the progression of HNSCC (139). Hyperactivation of YAP/TAZ is associated with the expansion of HNSCC stem cells and treatment resistance (140,141). Physiologically, the Hippo pathway is normally active (Hippo ON), and LATS1/2 kinases are phosphorylated and activated by macrophage stimulating 1 (MST1) and MST2, serine/threonine protein kinases (142). Subsequently, LATS1/2 kinases phosphorylate the transcriptional coactivator YAP and TAZ, ultimately leading to nuclear exclusion of YAP/TAZ, causing apoptosis and limiting excessive organ growth (142,143). YAP and TAZ translocate to the nucleus when the core Hippo kinases are inactive (Hippo OFF) and bind to the TEA domain transcription factor family to promote cell growth and proliferation or interact with other transcription factors or signaling molecules (144). Hyperactivation of YAP and TAZ may contribute to the development of multiple types of tumors (145). In this section, the role of ubiquitination modifications in regulating the Hippo pathway were summarized.

*UCHL3.* UCHL3, a member of the USPs family, plays an important role in protein degradation (146). It has been reported that UCHL3 is involved in several biological processes, including DNA repair, fertilization, the development of preimplantation embryos, osteoblast differentiation, and tumor progression (147-151). Recently, Tang *et al* (152) discovered that UCHL3, a novel YAP deubiquitinating enzyme, regulates YAP deubiquitination and stabilization in anaplastic thyroid cancer. Another study showed that UCHL3 stabilizes and maintains YAP by interacting with the WW domain of YAP to delete K11- and K48-linked ubiquitin chains (152). Collectively, UCHL3 can promote cancer progression and metastasis, indicating that UCHL3-specific inhibitors may have great therapeutic potential in HNSCC (152).

#### *Other DUBs*

*USP14.* USP14, a member of the USPs family, also serves as a novel biomarker in HNSCC and participates in various canonical cellular signaling pathways, including the NF- $\kappa$ B and Wnt/ $\beta$ -catenin signaling pathways (153,154). In multiple malignant tumors, USP14 expression is anomalous, including colorectal, ovarian, prostate, lung and liver cancer (155-159). Wang *et al* (153) discovered that USP14 overexpression is strongly associated with cancer metastasis and tumor stage in patients with HNSCC and found that USP14 physically interacts with heat shock transcription factor 1 (HSF1) and

stabilizes HSF1 through its deubiquitination. HNSCC is often exposed to the body's internal environment and lifestyle factors such as consuming betel nuts, smoking or drinking alcohol, which causes a heat shock response and stabilizes tumor cells, promoting the metastasis, invasion, migration and proliferation of tumor cells (153). As an oncogenic protein, HSF1 is an important transcription factor that maintains protein homeostasis in HNSCC (160,161). Wang *et al* (153) suggested that USP14 controls HSF1 stabilization by deubiquitinating it and increasing its downstream proteins, thereby leading to the proliferation of cancer cells and poor prognosis in patients with HNSCC. In summary, these findings consistently indicate that USP14 is a potential therapeutic target in HNSCC.

**USP9X.** The programmed death-1 (PD-1) PD-1/programmed death ligand 1 (PD-L1) pathway acts as an important regulator of tumor formation, and activation of this pathway may inhibit the activation and proliferation of T cells and promote the production of regulatory T cells, allowing tumor cells to escape recognition and killing by the immune system (162,163). A recent study demonstrated that the PD-1/PD-L1 pathway is aberrantly activated in HNSCC tissues, leading to tumor immunosuppression (164,165).

USP9X is a member of the largest family of USPs that regulate several signaling pathway components and various biological processes, including cell apoptosis, adhesion, proliferation, growth and migration (166-168). Furthermore, a series of studies have shown that USP9X has an important role in breast cancer, lung cancer, hepatocellular carcinoma and HNSCC (169-172). Recently, Wu *et al* (173) suggested that USP9X was associated with OSCC cell growth. Mechanistically, they found that USP9X deubiquitinated PD-L1 and stabilized its protein expression, thereby promoting immune escape of tumor cells in OSCC using immunohistochemistry, immunoprecipitation, western blotting, liquid chromatography-mass spectrometry and a T-cell-mediated tumor cell killing assay.

### 3. Treatment

**Traditional treatment of HNSCC.** The treatment of patients with HNSCC is complex and primary treatment modalities include surgery, radiotherapy and chemotherapy (27). Surgery is considered an effective treatment for oral cavity and early laryngeal cancers, while radiotherapy or concurrent chemoradiation is considered the standard treatment for other head and neck cancers (174,175).

Cetuximab, a monoclonal antibody targeting EGFR, was approved for combined radiotherapy for the treatment of patients with locally advanced HNSCC by the Food and Drug Administration in 2006 (4). For patients with recurrent or metastatic HNSCC, the extreme protocol, cetuximab, cisplatin or carboplatin, and 5-fluorouracil is recognized as the first-line therapy (2). Although cetuximab combined with chemotherapy/radiotherapy can lead to better efficacy in patients with HNSCC, improvements in the magnitude and duration of the clinical benefits are still needed (4,176).

Pembrolizumab (Keytruda) is an anti-PD-1 immune checkpoint inhibitor that has been widely used to treat a variety of malignancies (2). Pembrolizumab blocks the expression of PD-1 on tumor cells, thereby preventing tumor cells from

evading antitumor immunity (4). In 2019, pembrolizumab was approved for the first-line treatment for HNSCC (177,178).

The PI3K pathway is one of the most frequently mutated pathways in HNSCC and is associated with tumorigenic processes, making it an attractive target for cancer therapy (179). Currently, several drugs that target members of the PI3K pathway are in clinical trials. Buparlisib is a class I PI3K inhibitor that can inhibit the activity of various PI3K isoforms, and the combination of buparlisib and cetuximab has a synergistic antitumor effect (180). In addition, rapamycin, Copanlisib and Everolimus have also been reported (181-183). In the future, the PI3K pathway may be a promising target for the treatment of HNSCC.

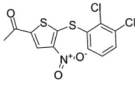
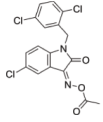
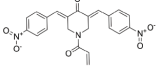
**Targeting deubiquitinase for HNSCC therapy.** Previous studies have shown that members of the DUB family are aberrantly expressed in various malignant tumors (184). Numerous DUBs control apoptotic and proliferative processes in cells, and compared to proteasome inhibition, therapeutic targeting of DUBs has lower cytotoxicity and better therapeutic efficacy (18). Hence, it is a potential target for cancer therapies. Vif1 and vif2 are USP7 inhibitors that have the potential to be molecularly targeted agents for laryngeal cancer (185). Mechanistically, the vif1 peptide blocked the binding of cellular substrates to TRAF, while the vif2 peptide bound to the active catalytic sites of the TRAF and DUB structural domains of USP7, thereby inhibiting USP7 activity (185). Hu *et al* (186) discovered that P5091 is a selective and efficient USP7 inhibitor that can effectively suppress esophageal cancer cell growth via the ATF4/NOXA apoptotic pathway.

HIF-1 $\alpha$  is considered a well-established pro-metastatic factor that can be activated by the viral oncogene latent membrane protein 1 (LMP1) and transferred to nasopharyngeal carcinoma-associated LMP1-positive exosomes (187,188). LDN-57444 is a small-molecule inhibitor of UCHL1. Kobayashi *et al* (189) found that LDN-57444 has anti-metastatic effects in cell lines of OSCC and nasopharyngeal carcinoma and that LDN-57444 inhibits exosomes and levels of pre-metastatic factors by inhibiting UCHL1 activity. Taken together, LDN-57444 could reduce the level of metastatic markers, inhibit the metastasis of LMP1 and decrease the adhesion of cancer cells, and may provide promising therapeutic potential for Epstein-Barr virus-positive malignancies (189).

b-AP15 is a new small-molecule USP14 inhibitor. Treatment with b-AP15 inhibits tumorigenesis in multiple cancers, including colorectal cancer, lymphoma, lung cancer and breast cancer (190-193). Tian *et al* (193) discovered that b-AP15 inhibits cell proliferation and induces endogenous apoptosis and cell cycle arrest by promoting the accumulation of high-molecular-weight polyubiquitin proteins. In tongue cancer, b-AP15 targets DUBs to overcome bortezomib resistance (Table II).

**DUBTAC.** The use of Proteolysis-Targeting Chimeras to target the degradation of numerous disease-causing proteins in cells offers a potentially promising therapeutic strategy for cancer treatment and several projects are currently in clinical development (194). However, the degradation of aberrant proteins is also a causative mechanism in certain diseases, therefore targeting deubiquitinase chimeras (DUBTAC) to mediate

Table II. Summary of inhibitors targeting deubiquitinating enzymes in head and neck squamous cell carcinoma.

Targets	Compound	Mechanism of action	Molecular structure	(Refs.)
USP7	vif1/vif2	Blocks USP7, leading to p53-dependent cell-cycle arrest and apoptosis in culture	-	(185)
	P5091	Suppresses cancer cell growth via the ATF4/NOXA apoptosis pathway		(186)
UCHL1	LDN-57444	Reduces pro-metastatic markers, carcinoma cell adhesion and transfer of LMP1		(189)
USP14	b-AP15	Regulation of apoptosis and cell cycle progression and activation of the unfolded protein response		(193)

USP7, ubiquitin-specific protease 7; UCHL1, ubiquitin carboxyl terminal hydrolase L1; LMP1, latent membrane protein1; ATF4, activating transcription factor 4; NOXA, PMA-induced protein 1.

the recruitment of DUB and avoid the degradation of target proteins has become a new therapeutic strategy (195).

DUBTAC belongs to a family of targeted covalent inhibitors, which consists of DUB recruiters and protein of interest ligands (196). In a recent study, Henning *et al* (196) identified two distinct targets: The cystic fibrosis transmembrane conductance regulator (CFTR) and the WEE1 kinase. Transcoding mutations in CFTR (DF508) are the most common cause of cystic fibrosis and the authors used lumacaftor, a drug that has an affinity with DF508-CFTR, conjugated to the OTUB1 recruiter, EN523, and inhibited CFTR degradation, partially restoring the function of CFTR. In numerous cancers, WEE1 is degraded to promote cancer cell proliferation. The second DUBTAC consists of the WEE1 inhibitors AZD1775 and EN523. Studies have shown that this DUBTAC stabilizes the levels of WEE1 kinase in cancer cells, thus promising to stop tumor growth (196,197).

However, DUBTAC technology is still in the early stages of development, and the safety of drugs developed based on DUBTAC remains to be determined. In addition to the two diseases mentioned above, there are many other diseases that could be stabilized by DUBTAC to gain a therapeutic benefit.

#### 4. Conclusions and prospects

HNSCC is a complex disease, and due to the insidious nature of its development, the majority of patients are found to be in a locally advanced stage with poor therapeutic outcomes. With the development of precision medicine, targeted therapies are gaining attention and may bring more options for patients with HNSCC. The aberrant expression of DUBs may be involved in tumorigenesis, progression and eventually metastasis, including HNSCC, by affecting the transduction of cellular signaling pathways. Current studies have shown that DUBs can modulate the levels of proteins insensitive to conventionally targeted therapies, so they have been considered a promising anti-tumor target. This review summarized DUBs in multiple

pathways linked to the development of HNSCC, including the p53 signaling pathway, NF- $\kappa$ B signaling pathway and PI3K signaling pathway, aiming to providing new ideas for the clinical treatment of HNSCC in the future.

Compared with previous proteasome inhibitors, DUB inhibitors are able to target specific DUBs to selectively block protein degradation, thereby reducing drug resistance and toxicity. However, DUB inhibitors are still in the developmental stage and are generally in preclinical studies, and more than half of them are multi-targeted inhibitors, with the biological mechanisms of DUBs related to tumors not yet fully clarified. Currently, the research on DUBs is progressing further, and it is esteemed that in the future, highly efficient and specific small-molecule DUB inhibitors will bring more therapeutic choices to patients.

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#### Availability of data and materials

Not applicable.

#### Authors' contributions

JW conceptualized the study, wrote the original draft, wrote the review and edited the manuscript. LW conceptualized the study, wrote the review and edited the manuscript. JC

provided the funding and revised and edited the manuscript. ZT revised and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

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### Competing interests

The authors declare that they have no competing interests.

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