Evolving role of deubiquitinating enzymes in oral cancer (Review)

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Abstract. Oral cancer affects the mucosal epithelium located within the oral cavity. The prevalence of oral cancer is projected to increase by ~40% by 2040, leading to a subsequent rise in mortality rates. Oral carcinogenesis is complex and multifactorial and numerous signaling pathways are involved in disease development. Deubiquitination is commonly involved in the post-translational process of proteins, and serves a key role in tumorigenesis and cancer development. The present review aims to discuss the function of deubiquitinating enzymes (DUBs) in oral cancer, with a particular focus on oral squamous cell carcinoma (OSCC). The present review also aims to investigate the functional mechanisms, tumorigenic regulation and therapeutic targets of DUBs in OSCC, which may potentially provide a novel theoretical basis for the utilization of DUBs as molecular targets in the treatment of OSCC in the future.

Contents

1. Introduction

Oral diseases rank highly amongst widespread health conditions worldwide, and impose notable health and economic burdens, which substantially diminish the quality of life of patients, impacting overall health and well-being (1). Oral cancer is a generic term used to refer to malignant tumors in oral organs. Notably, oral cancer encompasses cancer types of the lip, and all subsites of the oral cavity and oropharynx (2). According to the Global Cancer Statistics 2022, oral cancer was the 16th most common malignancy and the 15th leading cause of mortality worldwide (3), which was similar to the rankings observed in 2018 (4). The incidence of oral cancer is 2.72 cases per 100,000 individuals in China (men, 3.87; women, 1.60). Notably, the aforementioned rate is lower compared with the global incidence rate (men, 5.8; women, 2.3) (3,5). Oral squamous cell carcinoma (OSCC) is the most prevalent and extensively researched type of oral cancer, and the predominant malignancy within the head and neck region (6,7). In China, a total of 65,400 new cases of oral and pharyngeal cancer occurred in 2022 (5). The prevalence of oral cancer is projected to increase by ~40% by 2040 and this may lead to an increase in mortality rates in the future (5). Thus, numerous studies have focused on the molecular mechanisms underlying tumor growth, invasion, migration and distant metastasis, with the aim of identifying novel therapeutic targets and key tumor markers in OSCC. Previous studies have demonstrated that deubiquitinating enzymes (DUBs) serve an important role in the development of OSCC (8,9). The present review aims to investigate the functional mechanisms, tumorigenic regulation and therapeutic targets of DUBs in OSCC, which may provide a novel theoretical basis for the diagnosis and treatment of oral cancer in the future.

2. Oral carcinogenesis

In total, ~90% of oral cancer types originate in the stratified non-keratinized epithelium of the oral mucosa (10). Notably, oral cancer may be caused by genetic, epigenetic and environmental factors, including tobacco, alcohol and poor nutrition, which lead to changes in oral keratinocytessize and shape (10). Early genetic and molecular alterations of oral keratinocytes occur in all tissue areas exposed to carcinogens, followed by varying degrees of damage to the epithelium, which may lead to oral epithelial carcinoma and metastasis (Fig. 1) (11). A previous study has demonstrated that the development of OSCC may also be caused by additional factors, such as autoimmune diseases, infectious diseases, immunosuppressive

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disorders and familial cancer syndromes that modulate the immune system (12).

The key characteristics of oral cancer include sustained cellular proliferation, resistance to apoptosis, invasion and metastasis, dysregulation of energy homeostasis, evasion of growth inhibitory signals, and the ability to circumvent immunotherapeutic interventions (13). Oral carcinogenesis is complex and multifactorial, involving genetic mutations, epigenetic modifications and imbalances in the tumor microenvironment (TME). Genetic alterations may lead to the abnormal activation of oncogenic signaling pathways, including PI3K/AKT/mTOR (14,15), EGFR (16), Wnt/β-catenin (17), Notch (18) and JAK/STAT (19) pathways, and simultaneously disrupt tumor suppressor pathways, such as the tumour protein 53/retinoblastoma pathway (20). Notably, the aforementioned alterations serve a key role in the progression of OSCC. Furthermore, epigenetic modifications, such as DNA methylation (21), histone covalent modifications (22) and chromatin remodeling (23), are also implicated in the initiation and progression of OSCC. Additional factors such as immune suppression (24), hypoxia (25) and imbalances in the oral microbiome (26) may also contribute to the dysregulated TME, thus facilitating OSCC progression.

3. Diagnosis and treatment of oral cancer

In clinical practice, patients with OSCC may present with early-stage lesions that are painless. However, as OSCC progresses, lesions may cause ulceration, nodules and tissue adherence (27). In total, ~50% of OSCC cases arise in the posterior lateral border of the tongue, with the remaining cases affecting the floor of the mouth, soft palate, gingiva, buccal mucosa and hard palate (28). Oral cancer is detected in clinical examinations; however, >50% of patients with OSCC are diagnosed during the advanced stages of the disease (stages III and IV) and >40% of patients with OSCC present with regional metastases at the time of diagnosis (28). Furthermore, OSCC may invade the ipsilateral cervical lymph nodes through lymphatic outflow or invade the contralateral or bilateral lymph nodes. Notably, the lungs, bones and liver are the main sites of OSCC metastasis (29).

At present, surgery is the primary treatment option for OSCC; however, adequate resection margins are difficult to achieve due to the complex anatomy of the affected area (13). Ionizing radiation (IR), immunotherapy and chemotherapy may be used to prevent or treat OSCC (13). Thus, the identification of novel biomarkers and therapeutic targets in OSCC is necessary. A recent systematic review has summarized the hallmarks of oral cancer and highlighted the importance of further studies focused on OSCC (30). In addition, numerous mono-antibodies or small molecular compounds that inhibit tumorigenesis have been developed. PRI-724, a specific inhibitor of the Wnt/β-catenin signaling pathway, works synergistically with vismodegib, erlotinib and HS-173 to effectively decrease cell viability, promote apoptosis and decrease cell migration in OSCC (31). Cetuximab, an EGFR-targeting antibody, may be used to enhance the antitumor function of PI3K/AKT inhibitors (32). Current research on oral cancer focuses on the role of DUBs, which exhibit potential as molecular targets in the treatment of oral cancer (8,9).

4. Ubiquitination and deubiquitination

The sequential enzymatic processes that covalently attach ubiquitin, a 76-residue polypeptide with a molecular mass of ~8.5 kDa, to target proteins, are known as ubiquitylation. Ubiquitylation is achieved through a mechanism that involves several factors, including ubiquitin-activating enzyme (E1), ubiquitin-binding enzyme (E2) and ubiquitin ligase (E3). In humans, there are two variants of E1 enzymes, namely, ubiquitin-like modifier activating enzyme 1 and ubiquitin-like modifier activating enzyme 6, alongside ~50 distinct E2 enzymes and ~600 different E3 enzymes. Notably, E3 enzymes are pivotal in the selective identification of target proteins for ubiquitination and operate in a manner that is both spatially and temporally specific (33). Ubiquitin contains seven lysine residues and an N-terminal region that function as a site for ubiquitination, specifically at positions K6, K11, K27, K29, K33, K48, K63 and M1. Ubiquitin chains bind to substrates by linking the glycine residue of ubiquitin to a lysine molecule of ubiquitin (34). Different linkages exhibit different roles for the target substrate. Notably, K48-linked chains represent the most prevalent type of ubiquitin linkage within cellular environments, accounting for >50% of all ubiquitin linkages (33). The primary function of K48-linked chains is to facilitate the targeting of proteins to the proteasome for degradation. By contrast, K63-linked chains, which are the second most abundant type of ubiquitin linkages, exhibit a range of non-degradative functions (33). Ubiquitination serves a key role in numerous pathological conditions, such as neurodegenerative diseases, various cancers, aging and metabolic disorders (35). Alternate atypical ubiquitin modifications, linked through M1, K6, K11, K27, K29 or K33, also exhibit unique functions in substrate modification (36). Variations in the use of ubiquitin lysine residues may lead to the formation of homotypic chains, which are linked exclusively through a single type of residue, or heterotypic and branched chains. The aforementioned processes are exemplified by K63-linear and K48-K11 hybrid polymers, respectively (37).

DUBs are a class of proteases that facilitate the reversal of protein ubiquitination, a critical process for maintaining healthy cellular homeostasis. DUBs are responsible for the removal of ubiquitin from target proteins, which enables the recycling of ubiquitin, mediated by ~100 distinct DUBs (38). Ubiquitin molecules may be conjugated to the N-terminal amino group or lysine residues on other ubiquitin molecules, which results in the formation of ubiquitin chains (39). DUBs possess the ability to dismantle ubiquitin conjugations by cleaving the linkages between ubiquitin molecules or processing ubiquitin precursors to produce free pools of ubiquitin (Fig. 2A) (39). In total, there are ~100 DUBs that are classified into eight different families, namely, ubiquitin specific protease (USP), ubiquitin carboxy-terminal hydrolase, JAB1/MPN/MOV34 metalloenzyme, ovarian tumor protease (OTU), motif interacting with ubiquitin-containing novel DUB, monocyte chemotactic protein-induced proteins zinc finger-containing ubiquitin peptidase 1 and Machado-Joseph disease (Fig. 2B) (40,41). Furthermore, DUBs exhibit four

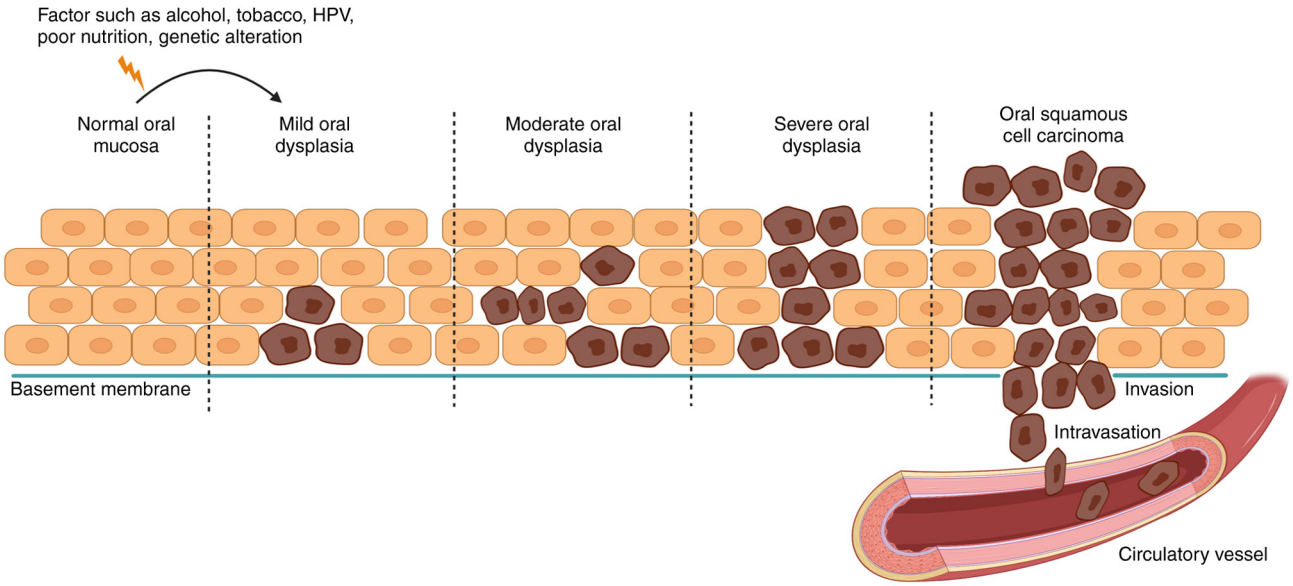

Figure 1. Schematic diagram of oral carcinogenesis. The normal oral mucosa is a layer of epithelial cells arranged on a basement membrane that separates the epithelium from connective tissue and blood vessels. When the oral mucosa is stimulated by internal and external factors (genetic alterations, tobacco, alcohol, poor nutrition), the deepest cells undergo changes in shape and size, known as oral dysplasia. Oral dysplasia, which can be classified into mild, moderate and severe, is considered to precede the development of OSCC and to be a notable predictor of malignant transformation. During OSCC development, massive phenotypic changes occur in all epithelial cell layers and extend towards the tissue boundaries with rupture of the basement membrane, which invades the connective tissue and binds to the blood vessels. OSCC, oral squamous cell carcinoma; HPV, human papillomavirus.

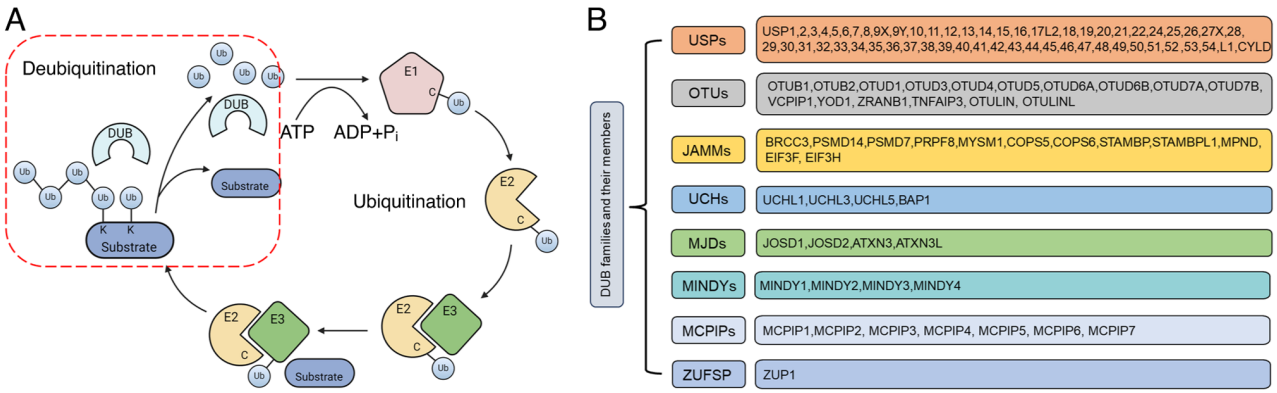

Figure 2. Ubiquitylation cascade and classification of DUB families. (A) Schematic diagram of key events in ubiquitylation and deubiquitylation. Under the condition that ATP provides energy, ubiquitin binds to the target protein (E1, E2, E3) through the cascade catalytic reaction. The DUBs cleave the monoubiquitin or polyubiquitin chains from ubiquitinated proteins. (B) Classification of DUB families and members. In total, ~100 DUBs are classified into eight different families. DUBs edit ubiquitin chains to exert either tumor-suppressive or oncogenic effects on target substrates, which is dependent on the DUB, context and substrate. DUB, deubiquitinating enzyme; Ub, ubiquitin; E1, ubiquitin-activating enzyme; E2, ubiquitin-binding enzyme; E3, ubiquitin ligase; USP, ubiquitin specific protease; UCH, ubiquitin carboxy-terminal hydrolase; JAMM, JAB1/MPN/MOV34; OTU, ovarian tumor protease; MJD, Machado-Joseph disease; MINDY, motif interacting with ubiquitin-containing novel DUB; MCPIP, monocyte chemotactic protein-induced proteins; ZUFSP, zinc finger-containing ubiquitin peptidase 1.

distinct mechanisms of action, namely, processing of ubiquitin precursors, recycling of ubiquitin molecules during ubiquitination, cleavage of poly-ubiquitin chains and reversal of ubiquitin conjugation (42). The aforementioned mechanisms are used to regulate several cellular functions, including cell cycle progression, vesicle transport, signal transduction and chromosome segregation (43). DUBs also serve key roles in various developmental processes of eukaryotic cells, including apoptosis (44), DNA damage repair (45), maintenance of cell stemness (46) and tumorigenesis (47). Thus, the association between ubiquitination and DUBs is essential for cellular homeostasis.

5. Deubiquitination in oral cancer

Numerous DUBs may be associated with either tumor-suppressive or oncogenic activities and exhibit potential as candidates for therapeutic intervention. Table I highlights key studies that focus on the regulatory mechanisms of DUBs in oral cancer under reference summarized.

Association between DUBs and the Wnt/β-catenin pathway in oral cancer. Under healthy conditions, the Wnt family of proteins bind to Frizzled receptor and related ligands such as LDL receptor-related protein 5/6 (LRP5/6) on the cell surface

Table I. Summary of previously published studies on DUBs in oral cancer.

First author/s, year	Oral cancer type	DUBs	Substrate	Summary of results	Prognosis	(Refs.)
Wu *et al*, 2018	OSCC	USP9X	PD-L1	USP9X combined with PD-L1 induced PD-L1 deubiquitination and stabilized PD-L1 protein expression in OSCC.	Poor	(8)
Sulkshane *et al*, 2021			MCL1	USP9X interacted with and deubiquitinated MCL1, stabilizing MCL1. The upregulation of USP9X and MCL1 was associated with poor prognosis in patients with OSCC.	Poor	(72)
Shinriki *et al*, 2018	OSCC	CYLD	ALK5	Knockdown of CYLD induced stabilization of TGF-β receptor I (ALK5) and promoted TGF-β signaling in a cell autonomous manner, which was associated with the clinical features of deep invasion and poor overall survival in invasive OSCC.	Good	(64)
Kanemaru *et al*, 2022			-	EGFR tyrosine kinase inhibitor gefitinib decreased the cell survival rate by inhibiting TGF-β signaling in cisplatin-resistant CYLD-knockdown OSCC cells.	Good	(65)
Suenaga *et al*, 2019			Cisplatin	Cisplatin resistance was mediated by CYLD downregulation. Cisplatin resistance was associated with a decrease in the accumulation of intracellular cisplatin and the inhibition of cisplatin-induced apoptosis via hyperactivation of the NF-κB signaling pathway.	Good	(80)
Li *et al*, 2023	OSCC	OTUB1	RACK1	Knockdown of OTUB1 suppressed cell proliferation, invasion, migration and xenograft tumor growth, and promoted tumor-associated macrophage M1 polarization but suppressed M2 polarization, which inhibited the survival of OSCC cells.	Poor	(73)
Liu *et al*, 2024			SLC7A11	TCF12 promoted ubiquitination of SLC7A11 and decreased SLC7A11 protein stability through transcriptional repression of OTUB1, thereby facilitating ferroptosis. TCF12 enhanced cisplatin sensitivity in OSCC cells by promoting ferroptosis, which was achieved by modulating SLC7A11 expression via transcriptional regulation of OTUB1.	Poor	(84)
Feng *et al*, 2020	OSCC	USP17	SNAI1	The direct binding between LINC02487 and the DUB USP17 inhibited cell migration and invasion through the USP17-SNAI1 axis in a process that involved epithelial-mesenchymal transition.	Good	(85)
Liu *et al*, 2024	OSCC	USP14	Sox2	USP14 knockdown impaired Sox2 stability by increasing its polyubiquitination. USP14 upregulation was associated with progression-free interval in patients with OSCC.	Poor	(74)
Zhang *et al*, 2024			PFKL	PFKL is a key rate limiting enzyme involved in the glycolytic pathway. The interaction between USP14 and PFKL improved the stability of PFKL in OSCC cells, which enhanced PFKL-mediated glycolytic metabolism, and promoted cellular proliferation, migration and tumorigenesis.	Poor	(75)

Table I. Continued.

First author/s, year	Oral cancer type	DUBs	Substrate	Summary of results	Prognosis	(Refs.)
Xie and Xu, 2021			LC3BI/II	USP14 knockdown promoted IR-induced autophagy via the upregulation of LC3BII and γH2AX expression levels in IR-treated OSCC cells.	Good	(81)
Lu *et al*, 2021	OSCC	USP18/ USP20	STING	Knockdown of STING, a verified substrate of USP18 and USP20, induced the multiplication of T1012G virus yields in SCC9 cells. The effects of GSK2643943A, a DUB inhibitor, targeting USP20 on viral replication and tumor death were evaluated, both *in vitro* and *in vivo*.	Poor	(86)
Kobayashi *et al*, 2019	OSCC	UCHL1	LMP1	UCH-L1 DUB inhibitors, LDN and LDN-POx, suppressed the motility of metastatic OSCC and nasopharyngeal cells expressing Epstein-Barr virus pro-metastatic LMP1 in physiological assays. Furthermore, treatment with LDN and LDN-POx resulted in decreased levels of pro-metastatic markers, a decrease in carcinoma cell adhesion, and inhibition of extracellular vesicle-mediated transfer of the viral invasive factor LMP1.	Poor	(87)
Chen *et al*, 2024	OSCC	USP44	HEXIM1	Upregulation of USP44 induced an increase in the stability of the HEXIM1 protein, which subsequently elevated HEXIM1 expression levels in OSCC. The silencing of HEXIM1 further exacerbated the malignant characteristics of OSCC cells. The knockdown of HEXIM1 negated the antitumor effects associated with USP44. USP44 functions as a crucial tumor suppressor in OSCC via inhibition of cell proliferation and metastasis through the stabilization of the HEXIM1 protein.	Good	(88)
Chang *et al*, 2022	SCC	OTUB2	STAT1	OTUB2 suppressed development and progression in tongue and esophageal SCCs. OTUB2 promoted the deubiquitination, phosphorylation and dimerization of STAT1, and induced the activation of CALML3/ Ca^{2+}/phosphatidy lserine signaling. Oral administration of soybean-derived phosphatidylserine inhibited SCC initiation and progression, which was associated with low OTUB2 expression.	Good	(89)

OSCC, oral squamous cell carcinoma; SCC, squamous cell carcinoma; DUB, deubiquitinating enzyme; USP9X, ubiquitin specific peptidase 9 X-linked; CYLD, cylindromatosis lysine 63 deubiquitinase; OTUB, OTU deubiquitinase, ubiquitin aldehyde binding; UCHL1, ubiquitin C-terminal hydrolase L1; PD-L1, programmed cell death-ligand 1; MCL1, myeloid cell leukemia-1; RACK1, receptor for activated C kinase 1; SLC7A11, solute carrier family 7 member 11; SNAI1, Snail family transcriptional repressor 1; PFKL, phosphofructokinase-1 liver type; Sox2, Sry-Box transcription factor 2; IR, ionizing radiation; STING, stimulator of interferon genes; LMP1, latent membrane protein 1; STAT1, signal transducer and activator of transcription 1; HEXIM1, hexamethylene bis-acetamide-inducible protein 1; ALK5, activin receptor-like kinase 5; LDN-Pox, low-dose naltrexone-Pox; TCF12, T-cell factor 12; CALML3, calmodulin-like protein 3.

to form a complex that recruits the protein framing protein, Dishevelled, which leads to the phosphorylation of LRP5/6 and the recruitment and activation of the Axin protein complex. In turn, the activation of the Axin protein complex inhibits the phosphorylation and degradation of β-catenin proteins and leads to stabilization. Accumulation of β-catenin in the cytoplasm will lead to entry into the nucleus spontaneously, where β-catenin binds to T cell factor/lymphoid enhancer factor family proteins, which promotes the transcription and expression of Wnt target genes, including Axin2, c-Myc and Cyclin D1. The expression levels of Wnt target genes serve a key role in cell proliferation, cycle regulation and differentiation. In the

absence of Wnt activation, β-catenin is phosphorylated by the Axin protein complex, where β-catenin binds to ubiquitin E3 ligase (β-Trcp) (48). β-Trcp is subsequently presented to the proteasome for ubiquitination (48). To date, numerous studies have focused on the role of Wnt in OSCC and demonstrated that components of the Wnt/β-catenin signaling pathway, including Wnt ligands, Wnt inhibitors, membrane receptors and intracellular mediators, serve a key role in the inhibition of OSCC (11,49,50).

A previous study has demonstrated that USP14 activates the Wnt downstream pathway by regulating the deubiquitination and subsequent phosphorylation of Dishevelled (51). In OSCC tissues, USP14 expression levels are markedly upregulated (52). Furthermore, *in vitro* cellular experiments and investigations using mice transplantation tumor models have demonstrated that the proliferation, invasion and migration of OSCC were inhibited following USP14 knockdown (52).

Association between DUBs and the NF-κB pathway in oral cancer. NF-κB is a transcription factor that is often located in the cytoplasm and NF-κB regulates the expression of various genes, impacting cellular physiology and pathology. Activation of the NF-κB signaling pathway is often achieved through IκB protein degradation and nuclear translocation of NF-κB proteins, which serve key roles in inflammatory responses, immune responses and cell survival. In the inactive state, the IκB protein forms a complex with NF-κB, which leads to the prevention of NF-κB nuclear translocation (53). When inflammatory factors or cytokines stimulate the cell, the IκB protein is ubiquitinated and degraded, which allows the release of NF-κB protein into the nucleus to regulate the transcription of target genes (IL-6, inducible nitric oxide synthase) (53). Activated NF-κB promotes OSCC migration, invasion and resistance to radiotherapy (54).

DUBs regulate the NF-κB signaling pathway, which leads to oncogenic and anti-oncogenic activity. Receptor-interacting protein 1 (RIP1) may be modified by K63-linked polyubiquitination, which leads to TNF-α-induced NF-κB activation, increased expression levels of anti-apoptotic proteins [cellular inhibitor of apoptosis protein-1/2, (cIAP1/2), Bcl-2] and the promotion of cell survival. The DUB USP4 exerts a regulatory effect on RIP1 and a previous study has demonstrated that USP4 was upregulated in OSCC (55). USP4 inhibits NF-κB activation and promotes apoptosis via cleavage of the K63 ubiquitin chain of RIP1, which leads to oncogenic activity (56). In addition, cylindromatosis lysine 63 deubiquitinase (CYLD) is a key negative regulator of NF-κB. CYLD specifically removes the K63 ubiquitin chain and the M1 linear ubiquitin chain, and inhibits NF-κB signaling within different pathways. Mutations or low expression levels of CYLD in OSCC result in abnormal activation of NF-κB and inhibition of TGF-β (57). Previous studies have also demonstrated that CYLD upregulation inhibited the invasion and metastasis of the SCC15 OSCC cell line (58,59).

Association between DUBs and the TGF-β pathway in oral cancer. Members of the TGF-β family exert cellular effects through the formation of heterotetrameric complexes, comprising type I and type II serine/threonine kinase transmembrane receptors. To date, five type II receptors and seven type I receptors, referred to as activin receptor-like kinases (ALKs), have been characterized. TGF-β and bone morphogenetic protein dimers induce the formation of a heterotetrameric complex between a specific type II receptor and a type I receptor, which leads to the transphosphorylation and subsequent activation of the type I receptor. Furthermore, type I receptors propagate signals into the cell through the phosphorylation of receptor-regulated SMADs, which form heteromeric complexes with SMAD4 (Co-SMAD) (60,61). Co-SMAD translocates to the nucleus and interacts with other transcription factors (p300/CBP, Snail), which leads to the regulation of gene transcription responses (60,61). TGF-β signal transduction pathways may elicit a variety of cellular responses, which serve a key role in embryonic development, maintenance of tissue homeostasis and the process of tumorigenesis (62,63).

Notably, CYLD knockdown induced stabilization of TGF-β receptor I (ALK5), which promoted TGF-β signaling in OSCC. Low CYLD expression levels may lead to increased phosphorylation of SMAD3, which is a key indicator for the activation of the TGF-β signaling pathway. Low CYLD expression was associated with poor overall survival of patients with invasive OSCC (64). In addition, results from a previous study have demonstrated that cell survival was markedly increased in cisplatin-resistant OSCC cells with CYLD knockdown, which was associated with activation of the TGF-β signaling pathway. EGFR tyrosine kinase inhibitors, such as gefitinib, may be used to decrease cell survival via inhibition of TGF-β (65).

Association between DUBs and the tumorigenesis of oral cancer. P53 is one of the most commonly mutated proteins in various cancer types and exhibits oncogenic activity in tumors. Notably, P53 is activated following cellular stress, which leads to the inhibition of cell cycle progression and induction of pro-apoptotic signaling (66). Murine double minute 2 (MDM2) is an E3 ubiquitin ligase that specifically binds to P53, which leads to ubiquitination and degradation of P53 proteins. Under healthy conditions, MDM2 regulates the stability of P53, which limits P53 activity and maintains low levels of protein expression. Following DNA damage, MDM2 is inhibited by DUBs, which induces the release of accumulated P53 and promotes P53 activity. In turn, P53 induces MDM2 gene expression, which forms a negative feedback loop known as the P53-MDM2 signaling pathway (67). In OSCC, P53 gene mutations result in a loss of the oncogenic function of P53 and the upregulation of P53 and MDM2, which are associated with poor prognosis in patients (68).

DUBs serve a key role in stabilizing P53. Notably, CYLD inhibits tumor growth by cleaving the K63 ubiquitination chain on P53, which indirectly removes the K48 chain and inhibits the ubiquitination degradation of P53 (69). Findings from previous studies have demonstrated that USP28 effectively removed the MDM2-catalyzed K48 ubiquitin chain from P53, which led to the stabilization of P53. However, transcription of USP28 was notably upregulated in OSCC. Another study has demonstrated that OSCC is often associated with mutations or genetic variations in P53 (70,71). Thus, USP28-mediated stabilization of P53 may be detrimental to patients with OSCC (70,71).

Notably, alternative mechanisms may also serve a role in DUB-regulated tumorigenesis. Programmed cell death-ligand 1 (PD-L1) is upregulated in OSCC and acts as an oncogene (8). Results from a previous study have demonstrated that ubiquitin-specific peptidase 9 X-linked (USP9X) interacted with PD-L1, which facilitated deubiquitination of PD-L1 and thereby enhanced the stability of protein expression, which may promote OSCC tumorigenesis (8). Furthermore, myeloid cell leukemia-1 (MCL1), an anti-apoptosis protein, is markedly upregulated in OSCC. MCL1 is also deubiquitinated by USP9X. Notably, pharmacological inhibition of USP9X may decrease MCL1 expression and induce cell death in OSCC (72). Another study also demonstrated that OTU deubiquitinase, ubiquitin aldehyde binding 1 (OTUB1) was positively associated with OSCC tumor stage. OTUB1 knockdown leads to the suppression of OSCC cell proliferation, invasion and migration, and promotes tumor-associated macrophage M1 polarization. However, OTUB1 knockdown leads to the suppression of M2 polarization, which, in turn, inhibits the survival of OSCC cells (73). Furthermore, USP14 knockdown suppresses OSCC cell proliferation *in vitro* and tumor growth *in vivo*, due to impaired Sox2 stability mediated by polyubiquitination. Additionally, USP14 interacts with phosphofructokinase-1 liver type (PFKL), a key rate-limiting enzyme in the glycolytic pathway, which enhances PFKL-mediated glycolytic metabolism, and ultimately promotes cellular proliferation, migration and tumorigenesis (74,75).

Association between DUBs and the treatment of oral cancer. Treatment of OSCC requires a multidisciplinary approach, which often consists of surgical resection of the primary lesion, followed by post-operative radiotherapy (76). Molecular targeted therapy is a novel therapeutic strategy, and at present, two types of drugs are approved by the Food and Drug Administration for the treatment of OSCC, namely, cetuximab and nabulizumab (77). A key determinant of mortality in patients with OSCC is the elevated incidence of recurrence following treatment. Numerous studies have indicated that the overall recurrence rate ranges from 28 to 44.5% (26,78,79). Cisplatin resistance is a major obstacle in the treatment of middle- and late-stage OSCC, which leads to recurrence, metastasis and a poor prognosis. Cisplatin resistance mediated by decreased CYLD expression is associated with the diminished accumulation of intracellular cisplatin and the inhibition of cisplatin-induced apoptosis, which occurs as a result of hyperactivation of the NF-κB signaling pathway (80). The tolerance of OSCC to radiotherapy also affects patient prognosis and IR may induce the apoptosis of tumor cells. In a previous study, USP14 was knocked down in nude mice bearing OSCC tumors. USP14 knockdown facilitated IR-induced autophagy via upregulation of LC3BII and γH2AX expression levels in OSCC cells subjected to IR (81).

6. Conclusions

Aberrant activation and expression of signaling pathway components are commonly observed in OSCC, which may promote tumor cell proliferation, invasion and metastasis, and inhibit apoptosis (82). Regulation of DUBs in OSCC is considered to be an important factor in the abnormal activation of signaling pathways (83-89). Notably, DUBs operate through four distinct mechanisms: i) The processing of ubiquitin protein precursors; ii) the retrieval of ubiquitin molecules during the ubiquitination process; iii) the cleavage of ubiquitin protein chains; and iv) the disassociation of ubiquitin proteins from substrate targets. According to the aforementioned functions, DUBs may reverse the ubiquitination of target proteins, thereby contributing to the equilibrium between ubiquitination and deubiquitination of substrate proteins (90). While DUBs are known to be involved in the initiation and progression of OSCC, the specific mechanisms and downstream effects of DUBs remain poorly understood. DUBs have a dual role in oral cancer. The upregulation of some DUBs, such as USP14 and USP9X, promotes tumor development, while the downregulation of others like CYLD is linked to tumor invasion and drug resistance. By regulating key pathways (Wnt/β-catenin, NF-κB, TGF-β and P53), DUBs influence tumor progression. Their expression levels correlate with patient prognosis, suggesting a potential as therapeutic targets. Clinically, DUBs can indicate the prognosis of invasive OSCC patients. Targeting DUBs may overcome treatment resistance, and some DUBs inhibitors might enhance therapeutic effects when combined with other treatments. Given their potential as therapeutic targets in the treatment of OSCC, further research is warranted to elucidate the regulatory mechanisms associated with DUBs and to assess the potential side effects of targeted therapies.

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Authors' contributions

WY and FL conceived and organized the manuscript. ZW, SC and JW wrote the manuscript. JH revised the manuscript for important intellectual content. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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