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Ubiquitination and Deubiquitination in Oral Squamous Cell Carcinoma: Potential Drug Targets*

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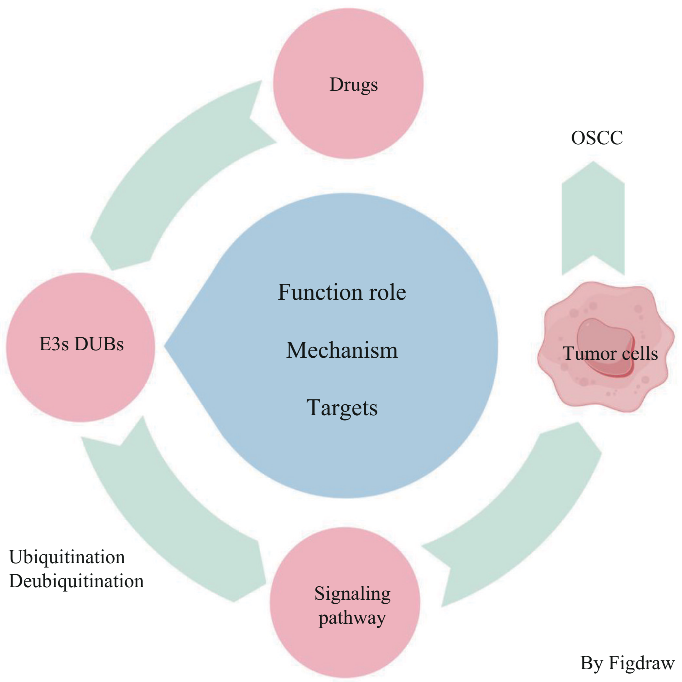
Graphical abstract



Abstract Oral squamous cell carcinoma (OSCC) is the most common head and neck malignancy worldwide, accounting for more than 90% of all oral cancers, and is characterized by high invasiveness and poor long-term prognosis. Its etiology is multifactorial, involving tobacco use, alcohol consumption, and human papillomavirus (HPV) infection. Oral leukoplakia and erythroplakia are the main precancerous lesions lesions, with oral leukoplakia being the most common. Both OSCC and premalignant lesions are closely associated with aberrant activation of multiple signaling pathways. Post-translational modifications

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(such as ubiquitination and deubiquitination) play key roles in regulating these pathways by controlling protein stability and activity. Growing evidence indicates that dysregulated ubiquitination/deubiquitination can mediate OSCC initiation and progression *via* aberrant activation of signaling pathways. The ubiquitination/deubiquitination process mainly involves E3 ligases (E3s) that catalyze substrate ubiquitination, deubiquitinating enzymes (DUBs) that remove ubiquitin chains, and the 26S proteasome complex that degrades ubiquitinated substrates. Abnormal expression or mutation of E3s and DUBs can lead to altered stability of critical tumor-related proteins, thereby driving OSCC initiation and progression. Therefore, understanding the aberrantly activated signaling pathways in OSCC and the ubiquitination/deubiquitination mechanisms within these pathways will help elucidate the molecular mechanisms and improve OSCC treatment by targeting relevant components. Here, we summarize four aberrantly activated signaling pathways in OSCC—the PI3K/AKT/mTOR pathway, Wnt/β-catenin pathway, Hippo pathway, and canonical NF-κB pathway—and systematically review the regulatory mechanisms of ubiquitination/deubiquitination within these pathways, along with potential drug targets. PI3K/AKT/mTOR pathway is aberrantly activated in approximately 70% of OSCC cases. It is modulated by E3s (*e. g.*, FBXW7 and NEDD4) and DUBs (*e. g.*, USP7 and USP10): FBXW7 and USP10 inhibit signaling, while NEDD4 and USP7 potentiate it. Aberrant activation of the Wnt/β-catenin pathway leads to β-catenin nuclear translocation and induction of cell proliferation. This pathway is modulated by E3s (*e.g.*, c-Cbl and RNF43) and DUBs (*e.g.*, USP9X and USP20): c-Cbl and RNF43 inhibit signaling, while USP9X and USP20 potentiate it. Hippo pathway inactivation permits YAP/TAZ to enter the nucleus and promotes cancer cell metastasis. This pathway is modulated by E3s (*e.g.*, $CRL4^{DCAF1}$ and SIAH2) and DUBs (*e.g.*, USP1 and USP21): $CRL4^{DCAF1}$ and SIAH2 inhibit signaling, while USP1 and USP21 potentiate it. Persistent activation of the canonical NF-κB pathway is associated with an inflammatory microenvironment and chemotherapy resistance. This pathway is modulated by E3s (*e.g.*, TRAF6 and LUBAC) and DUBs (*e.g.*, A20 and CYLD): A20 and CYLD inhibit signaling, while TRAF6 and LUBAC potentiate it. Targeting these E3s and DUBs provides directions for OSCC drug research. Small-molecule inhibitors such as YCH2823 (a USP7 inhibitor), GSK2643943A (a USP20 inhibitor), and HOIPIN-8 (a LUBAC inhibitor) have shown promising antitumor activity in preclinical models; PROTAC molecules, by binding to surface sites of target proteins and recruiting E3s, achieve targeted ubiquitination and degradation of proteins insensitive to small-molecule inhibitors, for example, PU7-1-mediated USP7 degradation, offering new strategies to overcome traditional drug limitations. Currently, NX-1607 (a Cbl-b inhibitor) has entered phase I clinical trials, with preliminary results confirming its safety and antitumor activity. Future research on aberrant E3s and DUBs in OSCC and the development of highly specific inhibitors will be of great significance for OSCC precision therapy.

Key words oral squamous cell carcinoma, ubiquitination, deubiquitination, drug targets
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Oral cancer is one of the most common malignant tumors globally, ranking 13th among the most prevalent cancers worldwide, with an estimated 377 713 new cases and 17 757 deaths in 2020, the majority of which occur in Asia[1-2]. Oral squamous cell carcinoma (OSCC) accounts for over 90% of all oral cancers, with other types potentially originating from epithelial, connective tissue, minor salivary glands, lymphatic tissue, melanocytes, or metastasis from distant tumor cells. The etiology of OSCC is multifactorial, but the most common risk factors are smoking and alcohol consumption, with a higher prevalence in male patients, particularly with middle-aged and elderly men being the most susceptible population[3]. OSCC exhibits high invasiveness into surrounding tissues, leading to an unfavorable prognosis[4].

Common precancerous lesions of OSCC include leukoplakia, erythroplakia, oral submucous fibrosis (OSF), lichen planus, verrucous hyperplasia, and epithelial hyperplasia or hyperkeratosis. Among these, leukoplakia is the most common precancerous lesion, presenting as white patches on the oral mucosa. It may result from chronic irritation such as tobacco use, alcohol consumption, or chronic friction[5-6].

Both OSCC and precancerous lesions are closely related to intracellular signaling pathways in their occurrence and development. For instance, the phosphatidylinositol-3-kinases (PI3K)/ protein kinase B (AKT)/ mammalian target of rapamycin (mTOR) pathway, Wnt/β-catenin pathway, JAK/STAT pathway, and NOTCH pathway exhibit abnormal activation in

OSCC[7], and the functions of these pathways are regulated by the ubiquitin proteasome system (UPS).

Normally, there are two protein degradation pathways in human cells: one is the UPS, and the other is the lysosomal pathway[8]. UPS is responsible for approximately 80% of intracellular proteins[9], and consists of several components, including ubiquitin (Ub), E1 activating enzyme, E2 binding enzyme, E3 ligase, E4 ubiquitin chain assembly factor, 26S proteasome and DUB[10], as well as multiple steps, including polyubiquitination of substrates by E1 activating enzyme, E2 binding enzyme, and E3 ligase; degradation of ubiquitin chains by DUB, and degradation of ubiquitinated substrates by the 26S proteasome complex[11]. In these steps, E3 ligase is the key enzyme responsible for substrate recognition and ubiquitination, while DUBs do the reverse by removing these Ub tags. Among all the types of ubiquitin chains, the K48-linked ubiquitin chain is the most classic degradation signal, mediating protein degradation through the 26S proteasome pathway[12]. In addition, the K48/K11 mixed chains work together to mediate the degradation of misfolded proteins, while the K29/K48 branched chains act in concert to enhance the efficiency of proteasomal degradation[13-14]. Moreover, other types of linkages are mainly associated with non-degradative ubiquitination. For example, the K6-linked ubiquitin chain plays roles in a variety of cellular processes, including DNA damage repair, cell cycle and mitochondrial quality control. The K27-linked ubiquitin chain is involved in the ubiquitination of the Parkinson's disease-related protein LRRK2[15]. The K33, K27, K29, and K63 mixed ubiquitin chains all participate in the activation of autophagy[16]. While the K63-linked ubiquitin chain is mainly involved in signal transduction[17], and the M1 linear ubiquitin chain is involved in modifying key proteins in the NF-κB pathway, leading to its activation[18]. Aberrant expression or mutation of E3 ligase and DUB can lead to the unbalanced ubiquitination, thus contributing to OSCC occurrence and development. Thus, drugs targeting E3s and DUBs which could balance the UPS may be promising molecules for the OSCC treatment.

In summary, it is crucial to understand the aberrant ubiquitination induced abnormal signaling pathways in OSCC, the underlying mechanism of UPS dysregulation, and promising drugs targeting E3s and DUBs. Therefore, this review figures out to explore the abnormal signaling pathways in OSCC, hoping to provide the ideas for the treatment of OSCC by targeting E3s and DUBs.

1　Abnormal pathways in OSCC

The occurrence of OSCC is a multistep process, regulated by multiple signaling pathways. Here, we focus on the 4 most extensively studied pathways, namely the PI3K/AKT/mTOR pathway, Wnt/β-catenin pathway, Hippo pathway, and canonical NF-κB pathway. Many E3s and DUBs modulate these pathways. Related E3s and DUBs are listed in Table 1, and their specific associations with each pathway are illustrated in Figure 1, 2. Notably, some E3s and DUBs, well-studied for their regulatory roles, show promise as therapeutic targets and will be elaborated on.

1.1　PI3K/AKT/mTOR pathway

PI3K/AKT/mTOR pathway is mainly composed of PI3K, AKT, mTOR, and phosphatase and tensin homolog (PTEN). The activation signals of PI3K can originate from various growth factors, cytokines, and insulin. Activated PI3K is recruited to the plasma membrane where it phosphorylates phosphatidylinositol 4,5-diphosphate (PIP2) to produce phosphatidylinositol 3, 4, 5-triphosphate (PIP3) [19-20]. Subsequently, inactive AKT in the cytosol is recruited to the plasma membrane, where phosphatidylinositol-dependent protein kinase 1 (PDK1) mediates the phosphorylation of AKT at T308 site, or the mammalian target of rapamycin complex 2 (mTORC2)-induced phosphorylation at S473, leading to the complete activation of AKT. This phosphorylation activation of AKT would regulate cell proliferation, differentiation, apoptosis, and migration[21]. On the other hand, PTEN can dephosphorylate PIP3, converting it back to PIP2, thus preventing the activation of AKT and inhibiting this signaling pathway[22].

Emerging studies have indicated that the activation of PI3K/AKT/mTOR pathway is commonly present in OSCC. Abnormal expression of components within this pathway, such as the aberrant activation of membrane receptors, mutations or amplifications of related kinases, and reduced or inactivated levels of PTEN, all of which could contribute to the promotion of tumor cell proliferation and metastasis by activating this signal[23-25].

1.1.1 Regulation of PI3K/AKT/mTOR pathway by E3s

(1) FBXW7. F-box and WD repeat domain containing 7 (FBXW7) is a member of the F-box protein family and is involved in the formation of the Skp1-Cdc53/Cullin-F-box-protein complex. The SCF complex functions as an E3 ligase, and within this complex, FBXW7 recognizes the substrates through its CDC4 phosphodegron (CPD) motif[26]. Studies have indicated that, as a tumor suppressor, the expression levels of FBXW7 are significantly decreased in colorectal cancer (CRC), esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), and breast cancer[27-31]. Within the PI3K/AKT/mTOR pathway, FBXW7 mediates the K48-linked polyubiquitination and degradation of mTOR[32-33]. Rapamycin-insensitive companion of mTOR (RICTOR), a component of mTORC2, can also be recognized by FBXW7 for ubiquitination and degradation after phosphorylation at the T1695 site, thereby influencing downstream pathways and exerting its tumor suppressive function[34]. Some studies have found that low expression of FBXW7 is commonly found in OSCC and is associated with poor prognosis, indicating that FBXW7 plays an important role in the regulation of OSCC development[35-36].

(2) NEDD4. Neuronally expressed developmentally downregulated 4 (NEDD4), a member of the NEDD4 family, comprises 3 domains: the C-terminal HECT domain, the N-terminal C2 domain, and the central 2 to 4 double tryptophan residue (WW) domain[37]. Studies have shown that in NSCLC, NEDD4 can exert oncogenic effects by mediating the ubiquitination of PTEN[38]. Concurrently, NEDD4 can directly bind to the Myc oncoproteins including c-Myc and N-Myc, exerting tumor-suppressive effects through the ubiquitination and degradation of these oncoproteins[39]. Within the PI3K/AKT/mTOR pathway, NEDD4 interacts with PTEN through its WW domain, mediating the K48-linked polyubiquitination and degradation of PTEN, thereby facilitating tumor development[40-41].

1.1.2 Regulation of PI3K/AKT/mTOR pathway by DUBs

(1) USP7. Ubiquitin-specific protease 7 (USP7) belongs to the USP family. It contains 7 domains, including the N-terminal TRAF-like domain, the catalytic core domain, and 5 C-terminal ubiquitin-like domains (UBL1−5) [42]. USP7 plays a crucial role in various biological processes, including tumorigenesis, inflammatory responses, neurodegenerative diseases, and viral infections. In PI3K/AKT/mTOR pathway, overexpression of USP7 can remove the ubiquitin from monoubiquitinated PTEN protein, preventing PTEN from entering the nucleus[43]. Studies have shown that knockdown of USP7 can inhibit the proliferation, migration, and invasion of OSCC cells and promote cell apoptosis, indicating that USP7 plays an important role in the regulation of OSCC development[44].

(2) USP10. Ubiquitin-specific protease 10 (USP10) belongs to the USP family[45]. It contains a catalytic domain, a ubiquitin-binding domain (UBD), a ubiquitin-associated (UBA) domain, a ubiquitin-interacting motif (UIM), and a zinc finger ubiquitin-specific protease (ZnF-UBP) domain[46]. USP10 is frequently downregulated in human cancers, including lung cancer, gastric cancer, and CRC[47]. However, studies have shown that high expression of USP10 is associated with poor prognosis in patients with head and neck squamous cell carcinoma (HNSCC). In the PI3K/AKT/mTOR pathway, USP10 can enhance the activity of PTEN by removing the K63-linked polyubiquitin chain, thereby reducing the production of PIP3 and exerting its tumor suppressor function. This action is in opposition to the K63-linked polyubiquitination mediated by TRIM25[48-49].

1.2 Wnt/β−catenin pathway

Wnt/β-catenin pathway is primarily composed of Wnt proteins, Wnt receptors, β-catenin, Dishevelled (DVL), destruction complex (DC), and T-cell factor/lymphoid enhancer factor (TCF/LEF). Among these, Wnt proteins include Wnt3a, Wnt1, and Wnt5a. The Wnt receptors mainly consist of the specific seven-pass transmembrane receptor Frizzled protein (FZD) and low-density lipoprotein receptor-related protein 5/6 (LRP5/6). The destruction complex is constituted by AXIN, APC, CK1α, GSK3β, and the E3 ligase β-TrCP[50-51].

When Wnts are present, Wnt proteins bind to FZD and LRP5/6, leading to the dimerization of the two receptors[52]. The cytoplasmic tail of LRP5/6, after being phosphorylated by several protein kinases, recruits the DC to the cell membrane. Concurrently, the cytoplasmic part of FZD can bind to DVL, participating in the recruitment of DC[53]. The DC loses its ability to degrade β-catenin, allowing β-catenin to translocate to the nucleus. There, it interacts with TCF/LEF to activate the transcription of target genes, thereby promoting cell proliferation and inhibiting apoptosis[54]. In the absence of Wnts, CK1α and GSK3β phosphorylate β-catenin, inducing its ubiquitination and degradation, thus blocking downstream responses[55-56].

During the development of OSCC, the accumulation and localization of β-catenin in the nucleus are associated with the malignancy of the tumor. In oral precancerous lesions, as the severity of the lesion increases, the nuclear localization of β-catenin gradually increases[57]. The secretion of Wnt ligands plays a crucial role in the occurrence of oral cancer. For example, the expression of Wnt3a increases in leukoplakia and is associated with the activation of β-catenin.

1.2.1 Regulation of Wnt/β-catenin pathway by E3s

(1) c-Cbl. Casitas B lineage lymphoma (c-Cbl) is a multifunctional protein, a member of the CBL protein family[58], possessing ubiquitin E3 ligase activity and comprising 5 domains: a tyrosine kinase binding (TKB) domain, a linker domain, a RING domain, a proline-rich (PR) domain, and a UBA domain[59]. Among these, phosphorylation of Y371 in the linker helix region (LHR) can influence the ubiquitination activity of c-Cbl. Phosphorylation of Y371 increases the affinity of c-Cbl for E2 binding enzyme, thereby enhancing the ubiquitination activity of c-Cbl[60]. In the Wnt/β-catenin pathway, in the absence of Wnts, c-Cbl targets cytoplasmic β-catenin and mediates its K48-linked polyubiquitination and degradation[61-62]. In the presence of Wnts, activation of the Wnt/β-catenin pathway promotes phosphorylation of the Y731 site of c-Cbl, leading to nuclear translocation of c-Cbl and degradation of nuclear β-catenin[63].

(2) RNF43. Ring finger protein 43 (RNF43) belongs to the GOLIATH/GRAIL family and consists of 5 domains: the protease-associated (PA) domain, the transmembrane domain, the RING domain, the disordered interaction (DIR) domain, and the casein kinase 1 binding and phosphorylation domain[64-65]. RNF43 was initially found to be overexpressed in CRC[66]. In 2012, it was discovered that RNF43 and its homolog ZNRF3 can mediate the ubiquitination of Wnt receptors, revealing their molecular mechanisms in cancer development[67-68]. Subsequently, an increasing number of studies have identified that mutations of RNF43 and ZNRF3 are associated with the occurrence of various cancers[69-71]. In Wnt/β-catenin pathway, RNF43 specifically mediates the polyubiquitination of lysines in the cytoplasmic loop of the Frizzled seven-transmembrane domain, ultimately exerting a tumor-suppressive effect[67].

1.2.2 Regulation of Wnt/β-catenin pathway by DUBs

(1) USP9X. Ubiquitin-specific peptidase 9 X-linked (USP9X) is a ubiquitin-specific peptidase associated with the X chromosome and is one of the highly conserved members of the USP family[72]. USP9X has two recognizable domains: the UBL domain and the catalytic domain with the USP characteristic cysteine and histidine catalytic motifs[73]. USP9X affects the stability and function of various substrates through its deubiquitination activity, playing an important role in cell signaling, tumor development, and neural development[74-76]. In Wnt/β-catenin pathway, it can interact with β-catenin and remove its K48-linked polyubiquitin chain, preventing β-catenin from being degraded by the proteasome[77]. In certain subtypes of OSCC, such as OSCC-GB, mutations in USP9X are common[78]. Meanwhile, high expression of USP9X is associated with shorter disease-free survival in OSCC[79].

(2) USP20. Ubiquitin-specific peptidase 20 (USP20) belongs to the USP family and contains 4 distinct domains, including the N-terminal ZnF-UBP domain, catalytic domain, and two tandem DUSP domains[80]. The DUSP domain is believed to be crucial for its deubiquitination activity, although its specific function is not fully understood[81]. It has been found that USP20 plays a role in cardiovascular diseases, tumorigenesis, and neurodegenerative diseases[82-84]. In Wnt/β-catenin pathway, USP20 can interact with β-catenin and remove its K48-linked polyubiquitin chains, preventing β-catenin from being degraded by the proteasome[85]. In OSCC, the expression level of USP20 is dramatically higher than that of adjacent non-cancerous tissues and normal oral tissues, and it is significantly associated with the differentiation degree and size of the primary tumor in OSCC[86]. It has been found that the use of the DUB inhibitor GSK2643943A targeting USP20 can

enhance the replication and cytotoxic effects of the T1012G virus in OSCC tumor cells, which shows that USP20 has great potential in the research and treatment of OSCC[87].

1.3 Hippo pathway

Hippo pathway is primarily composed of mammalian STE20-like kinase 1/2 (MST1/2), protein Salvador homolog 1 (SAV1), MOBKL1A/B (MOB1A/B), large tumor suppressor kinase 1/2 (LATS1/2), Yes-associated protein 1 (YAP), and WW-domain-containing transcription regulator 1 (TAZ)[88]. The Hippo pathway can be modulated by various upstream signals, such as cell polarity, mechanical cues, cell density, soluble factors, and stress signals[89]. At the core of Hippo pathway is a kinase cascade. MST1/2 can bind to the scaffold protein SAV1 through its C-terminal SARAH domain, and MST1/2 also promotes the binding of LATS1/2 to the scaffold protein MOB1A/B[90]. When the Hippo pathway is activated, MST1/2 and its scaffold protein SAV1 phosphorylate LATS1/2 and its scaffold MOB1A/B[91]. Phosphorylated MOB1A/B can further induce conformational changes in LATS1/2 increasing its activity[92], and thus activated LATS1/2 phosphorylates and inhibits YAP/TAZ, while also preventing their nuclear translocation[93]. When the Hippo pathway is not activated, YAP/TAZ translocate to the nucleus and bind to the transcription factors TEAD1−4 to induce gene expression, regulating cell proliferation, apoptosis, and stem cell self-renewal[94].

Recent studies have shown that in OSCC, the expression of MST2 decreases with the level of tumor differentiation degree, and at the same time, it has been found that high expression of YAP is closely related to the characteristics of epithelial-mesenchymal transition (EMT)[95-96].

1.3.1 Regulation of Hippo pathway by E3s

(1) $CRL4^{DCAF1}$. The Cullin 4-DDB1-Cullin associated factor 1 ($CRL4^{DCAF1}$) belongs to the CRL4 family and is a RING-type E3 ligase composed of CUL4A/B as the scaffold protein, DDB1 as the linker protein, and DCAF1 as the substrate recognition subunit[97]. DCAF1 is the key substrate receptor in $CRL4^{DCAF1}$ and contains 4 domains, namely a long Armadillo (ARM) domain, a LisH domain, a WD40 domain, and an acidic domain[98-99]. DCAF1 is involved in the regulation of various cellular processes, including the cell cycle, DNA repair, gene expression, cell proliferation, and apoptosis, and plays an important role in HIV infection and tumorigenesis[100]. In the Hippo pathway, it has been demonstrated that $CRL4^{DCAF1}$ can mediate the K48-linked polyubiquitination and degradation of LATS1/2 in the nucleus, thereby promoting the binding of YAP/TAZ and TEAD1−4, which in turn promotes cell proliferation and tumor formation[101].

(2) SIAH2. Seven in Absentia homolog 2 (SIAH2) belongs to the SIAH family and contains an N-terminal RING domain and a C-terminal Siah-binding domain (SBD) [102]. As an E3 ligase, SIAH2 plays crucial roles in various biological processes, including hypoxia response, cell cycle regulation, nervous system development, and immune microenvironment modulation[103-105]. In the Hippo signaling pathway, SIAH2 is activated under hypoxic conditions and mediates the K48-linked polyubiquitination and degradation of LATS2, promoting the nuclear translocation of YAP/TAZ and ultimately facilitating OSCC tumorigenesis[106].

1.3.2 Regulation of Hippo pathway by DUBs

(1) USP21. Ubiquitin-specific peptidase 21 (USP21) belongs to the USP family and contains a disordered N-terminal domain and a C-terminal catalytic domain responsible for catalytic activity. USP21 is involved in a variety of cellular processes, including apoptosis, DNA repair, and signal transduction[107]. Meanwhile, USP21 also plays an important role in tumor development, regulation of stem cell function, and immune regulation, especially in immune tolerance mediated by regulatory T cells[108-109]. In the Hippo pathway, USP21 can stabilize YAP protein by removing K48-linked polyubiquitin chains, thereby enhancing its activity and levels in cells[110]. In OSCC tissues, upregulation of USP21 expression is often observed, indicating that overexpression of USP21 promotes the development of OSCC[111].

(2) USP1. Ubiquitin-specific peptidase 1 (USP1) belongs to the USP family and is the founding member of this family[112]. Its structure comprises a catalytic domain consisting of an N-terminal cysteine box and two C-terminal histidine boxes, with C90, H593, and D751 forming the catalytic core[113-114].

USP1 plays a crucial role in maintaining genomic integrity, cell cycle progression, and cellular homeostasis[115]. In the Hippo pathway, USP1 interacts with the WW domain of TAZ, stabilizing TAZ by inhibiting its K11-linked polyubiquitination, thereby exerting a pro-tumorigenic effect[116].

1.4 Canonical NF−κB pathway

The canonical NF-κB pathway is mainly composed of NF-κB dimers, inhibitor of NF-κB (IκB), and IκB kinase (IKK). The NF-κB family consists of five members: p65, RelB, c-Rel, p50, and p52, among which p65/p50 is the most common dimerization form[117]. In the canonical NF-κB pathway, the p65/p50 heterodimer is responsible for the transcription of target genes. When the pathway is inactive, IκB proteins bind to the p65/p50 heterodimer and inhibit its nuclear translocation[118]. IKK is composed of two homologous catalytic subunits, IKKα and IKKβ, and a regulatory subunit NEMO. The canonical NF-κB signaling pathway is mainly activated by BCR, TCR, TLR, IL-1R, and TNFR. Among them, BCR and TCR initiate a multi-stage enzymatic reaction, activating the CARMA1/BCL-10/MALT1 complex. TLR, IL-1R, and TNFR mainly promote the activation of the TAK1/TAB complex. The activated CARMA1/BCL-10/MALT1 complex and TAK1/TAB complex phosphorylate the IKK. IKK induces the phosphorylation of IκB molecules promoting their ubiquitination and degradation, thus leading to the release of p65/p50, which acts as a transcription factor to activate the transcription of target genes promoting tumor formation and development[119]. Studies have shown that the target genes of NF-κB dimers including IκBα and IκBε, both of which are subunits of IκB. Newly synthesized IκBα protein binds to and drives the NF-κB dimer from the nucleus back to the cytosol[120].

Recent studies have shown that NF-κB is abnormally high levels of expression in OSCC. Meanwhile, the regulation of some components in the NF-κB pathway, such as IκB and IKK, has been proven to affect the progression of OSCC[121-122].

1.4.1 Regulation of NF-κB pathway by E3s

(1) TRAF6. TNF receptor-associated factor 6 (TRAF6) is a member of the TNF receptor-associated factor family. The N-terminus of TRAF6 contains a RING domain and 5 zinc finger domains[123]. The C-terminus has a TRAF domain, which consists of a coiled coil and a conserved TRAF-C domain[124]. TRAF6 was initially discovered to be involved in the signal transduction of IL-1 and CD40[125-126]. With further research on TRAF6, it was found that it also has E3 ligase activity and can work with the Ubc13-uev1a E2 complex to generate K63-linked polyubiquitin chains, mediating the degradation of various proteins[127]. In the NF-κB pathway, TRAF6 mediates the polyubiquitination of NEMO at the K63 site, thereby activating IKK[128].

(2) LUBAC. Linear ubiquitin chain assembly complex (LUBAC) is the only E3 ligase complex discovered so far that catalyzes the synthesis of linear ubiquitin chains[129]. LUBAC consists of 3 key subunits: SHANK-associated protein interacting protein (SHARPIN), HOIL-1-like protein (HOIL-1L), and HOIL-1-interacting protein (HOIP). Among them, HOIL-1 and SHARPIN are responsible for recognizing and binding to substrate proteins, while HOIP belongs to the RING-Between-RING (RBR) family. It recruits ubiquitin-conjugating E2 binding enzymes through its RING domain and transfers ubiquitin from the E2 binding enzyme to the substrate to form linear chains through its RBR domain[130]. In the NF-κB pathway, LUBAC recognizes NEMO *via* HOIP and couples linear ubiquitin chains to NEMO. NEMO coupled with linear ubiquitin chains is recognized by another NEMO in the IKK, leading to the activation of IKK2 through dimerization and trans-autophosphorylation of kinases in different IKKs. Activated IKK2 phosphorylates IκB to activate NF-κB[131].

1.4.2 Regulation of NF-κB pathway by DUBs

(1) A20. A20, also known as TNF-α-induced protein 3 (TNFAIP3), possesses DUB activity at its N-terminus, which can mediate K63-linked deubiquitination. The C-terminal domain contains multiple repeats of the Cys2/Cys2 ZnF motif[132-133]. It can remove K63-linked polyubiquitin chains from adaptor proteins such as RIP1, thereby preventing the activation of the IKK and subsequently inhibiting the nuclear translocation of NF-κB. Meanwhile, *A20* gene is one of the target genes of NF-κB. After NF-κB is activated, it can induce the expression of *A20*, which in turn can inhibit the activity of NF-κB, forming a

negative feedback regulatory loop[134]. In OSCC, inactivation of *A20* gene is relatively common, indicating that A20 plays an important role in the suppression of OSCC[135].

(2) CYLD. Cylindromatosis (CYLD) belongs to the USP family and contains 3 cytoskeleton-associated protein-glycine-rich (CAP-Gly) domains and one catalytic domain[136-137]. CYLD plays an important role in tumor suppression, neurodegenerative diseases, inflammation, and immune response[138-140]. In the NF-κB pathway, CYLD blocks the activation of NF-κB by removing the K63 ubiquitination of key proteins such as TRAF2, TRAF6, and NEMO[141]. In OSCC, CYLD knockout OSCC cells develop resistance to all existing cytotoxic chemotherapeutic drugs, including cisplatin, 5-FU, carboplatin, docetaxel, and paclitaxel[142-143].

Table 1 Summary of E3s and DUBs regulation in OSCC−related abnormal activation pathways

Pathway	Modified enzyme	Type of ubiquitination linkage	Binding domain	Target molecule	Regulatory effect	Reference
PI3K/AKT/mTOR pathway (E3s)	TRIM25	K63	B-box, CC, SPRY	PTEN	TRIM25 ubiquitination of PTEN inhibits its phosphatase activity	[48]
	FBXW7	K27	WD40	mTOR	FBXW7 mediates the ubiquitination and degradation of mTOR	[33]
	FBXL5	K48	FBX	PTEN	FBXL5 mediates the ubiquitination and degradation of PTEN	[144]
	NEDD4	K48	WW	PTEN	NEDD4 mediates the ubiquitination and degradation of PTEN	[40]
	Smurf1	–	WW	PTEN	Smurf1 mediates the ubiquitination and degradation of PTEN	[145]
	KLHL18	K48	Kelch	PI3K	KLHL18 mediates the ubiquitination and degradation of the PI3K p85α subunit	[146]
PI3K/AKT/mTOR pathway (DUBs)	USP7	monoUb	UBL	PTEN	USP7 mediates the ubiquitination of PTEN, thereby inhibiting its nuclear translocation	[147]
	USP10	monoUb	USP	PTEN	USP10 stabilizes the PTEN protein by deubiquitination, thereby reducing the production of PIP3	[147]
	USP11	K63	USP	PTEN	USP11 can stabilize the PTEN protein through deubiquitination	[147]
	USP13	K63	USP	PTEN	USP13 can stabilize the PTEN protein through deubiquitination	[147]
	USP14	K48	USP	PI3K	USP14 can directly deubiquitinate and activate PI3K	[148]
	OTUD3	K48	OTU	PTEN	OTUD3 can stabilize the PTEN protein through deubiquitination	[147]
Wnt/β-catenin pathway (E3s)	RNF43	–	TM	FZD	RNF43 mediates the polyubiquitination of lysines in the cytoplasmic loop of the FZD transmembrane domain	[67]
	ZNRF3	K48	TM	FZD	ZNRF3 antagonizes Wnt signaling by promoting the ubiquitination and degradation of the FZD receptor	[149]
	Cbl-b	K48	–	β-catenin	Cbl-b can mediate the ubiquitination and degradation of β-catenin	[58]
	c-Cbl	–	Generally PRY/SPRY domain	β-catenin	c-Cbl targets cytoplasmic β-catenin and mediates its ubiquitination and degradation	[150]
	β-TrCP	K48	WD40	β-catenin	β-TrCP can mediate the ubiquitination and degradation of β-catenin when the signaling pathway is inactivated	[151]

Continued to Table 1

Pathway	Modified enzyme	Type of ubiquitination linkage	Binding domain	Target molecule	Regulatory effect	Reference
Wnt/β-catenin pathway (DUBs)	CYLD	K63	CAP-Gly	DVL	CYLD negatively regulates signaling pathways by deubiquitinating DVL proteins	[152]
	USP7	K48	UBL	AXIN	USP7 mediates the ubiquitination and degradation of AXIN	[153]
	USP9X	K48	USP	β-catenin	USP9X can mediate the K48-linked polyubiquitination and degradation of β-catenin	[77]
	USP10	K48	USP	AXIN	USP10 can mediate the deubiquitination of AXIN, thereby affecting the stability of β-catenin	[154]
	USP15	K48	D1D2	β-catenin	USP15 can mediate the deubiquitination of β-catenin, thereby enhancing the stability of β-catenin	[155]
	USP20	K48	–	β-catenin	USP20 can mediate the deubiquitination of β-catenin, thereby enhancing the stability of β-catenin	[85]
Hippo pathway (E3s)	RNF146	–	WWE	AMOT	RNF146 mediates the ubiquitination and degradation of AMOT. The PPxY motif in AMOT interacts with the WW domain of YAP/TAZ, thereby binding to and inhibiting YAP/TAZ	[156]
	SIAH2	K48	The H150 region in SBD	LATS2	SIAH2 can mediate the polyubiquitination of LATS2, thereby promoting the nuclear translocation of YAP/TAZ	[106]
	WWP1	K48	WW	LATS1	WWP1 can mediate the ubiquitination and degradation of LATS1	[157]
	$CRL4^{DCAF1}$	K48	WD40	LATS1/2	$CRL4^{DCAF1}$ can mediate the ubiquitination and degradation of LATS1/2 in the cell nucleus	[101]
	β-TrCP	K48	WD40	YAP/TAZ	β-TrCP can mediate the ubiquitination and degradation of YAP/TAZ	[158]
	Fbxw7	K48	WD40	YAP	Fbxw7 can mediate ubiquitination and degradation of YAP	[159]
	ITCH	–	WW	LATS1/2	ITCH can mediate the ubiquitination and degradation of LATS1/2	[160]
Hippo pathway (DUBs)	USP1	K11	USP	TAZ	USP1 can mediate the degradation of TAZ with K11-linked polyubiquitin chains, thereby enhancing the stability of TAZ	[116]
	USP9x	–	USP	LATS2	USP9X can mediate the deubiquitination of LATS2, thereby maintaining the protein levels of LATS2	[161]
	USP21	K48	USP	YAP	USP21 can stabilize the YAP protein through deubiquitination	[110]
	OTUD1	K48	OTU	YAP	OTUD1 can stabilize the YAP protein through deubiquitination	[162]
	OTUB2	K48	OTU	YAP/TAZ	OTUB2 can bind to and activate YAP/TAZ	[163]
NF-κB pathway (E3s)	TRAF6	K63	TRAF-C	IKK	TRAF6 can mediate the K63-linked polyubiquitination of NEMO, thereby leading to the activation of IKK	[164]
	cIAP1/2	–	BIR	RIPK1	cIAP1/2 can mediate K63-linked ubiquitination of RIPK1, and this ubiquitination serves as a binding platform for the recruitment of the TAK1/TABs and NEMO/IKK complexes	[129]

Continued to Table 1

Pathway	Modified enzyme	Type of ubiquitination linkage	Binding domain	Target molecule	Regulatory effect	Reference
NF-κB pathway (DUBs)	LUBAC	Met1	NZF1	IKK	LUBAC can mediate the dimerization of IKK, thereby activating IκB	[131]
	XIAP	–	BIR	TAK1	XIAP can mediate the polyubiquitination of TAK1	[165]
	A20	K27	ZnF	IKK	A20 can remove K63-linked polyubiquitin chains from RIP1, thereby preventing the activation of the IKK complex	[134]
	CYLD	K63	CAP-Gly	TRAF2, TRAF6	CYLD can remove ubiquitination from TRAF2 and TRAF6, thereby blocking the activation of NF-κB	[141]
	OTUD1	K63	OTU	TAK1	OTUD1 can mediate the deubiquitination of TAK1	[166]

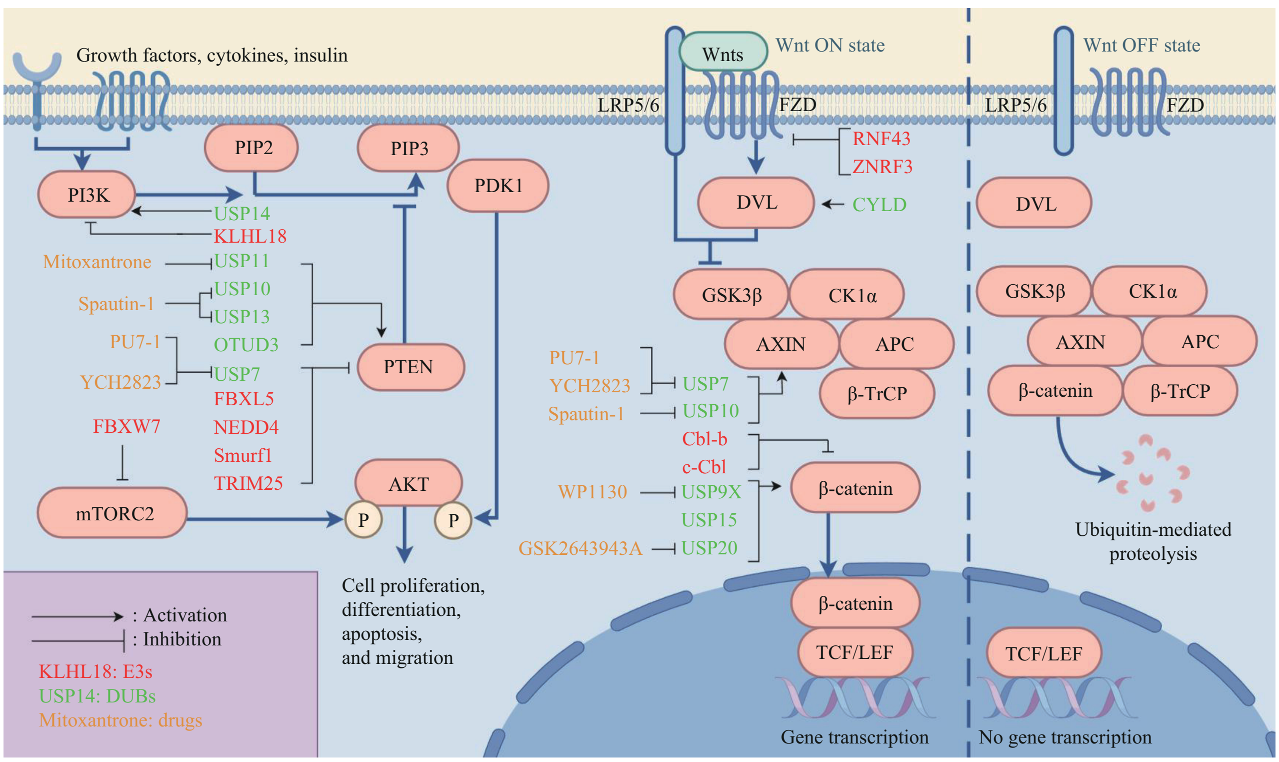


Fig. 1　The PI3K/AKT/mTOR and Wnt/β−catenin pathways and their current models of regulation by E3s and DUBs (by Figdraw)

Upon receiving extracellular activation signals, activated PI3K is recruited to the plasma membrane, where it phosphorylates PIP2 to generate PIP3. This recruits inactive AKT from the cytoplasm to the plasma membrane, driving PDK1 to phosphorylate the T308 site and mTORC2 to phosphorylate the S473 site, thereby fully activating AKT and regulating cell proliferation, differentiation, apoptosis, and migration. In this process, PTEN can dephosphorylate PIP3 back to PIP2, thereby preventing AKT activation and inhibiting the signaling pathway. The figure also illustrates the regulation of the PI3K/AKT/mTOR pathway by E3s and DUBs, as well as the modulation of this pathway by certain drugs targeting E3s and DUBs. When Wnts are present, Wnts bind to Frizzled protein (FZD) and LRP5/6, leading to the dimerization of both receptors. The cytoplasmic tail of LRP, after being phosphorylated by several protein kinases, recruits destruction complex (DC) to the cell membrane. Meanwhile, the cytoplasmic part of FZD can bind to Dishevelled (DVL), participating in the recruitment of DC. DC loses its ability to degrade β-catenin, which then translocates to the nucleus and activates the transcription of target genes through interaction with TCF/LEF, thereby promoting cell proliferation and inhibiting apoptosis. In the absence of Wnts, CK1α and GSK3β phosphorylate β-catenin, inducing its ubiquitination and degradation, which blocks downstream responses. The figure also illustrates the regulation of the Wnt/β-catenin pathway by E3s and DUBs, as well as the modulation of this pathway by certain drugs targeting E3s and DUBs.

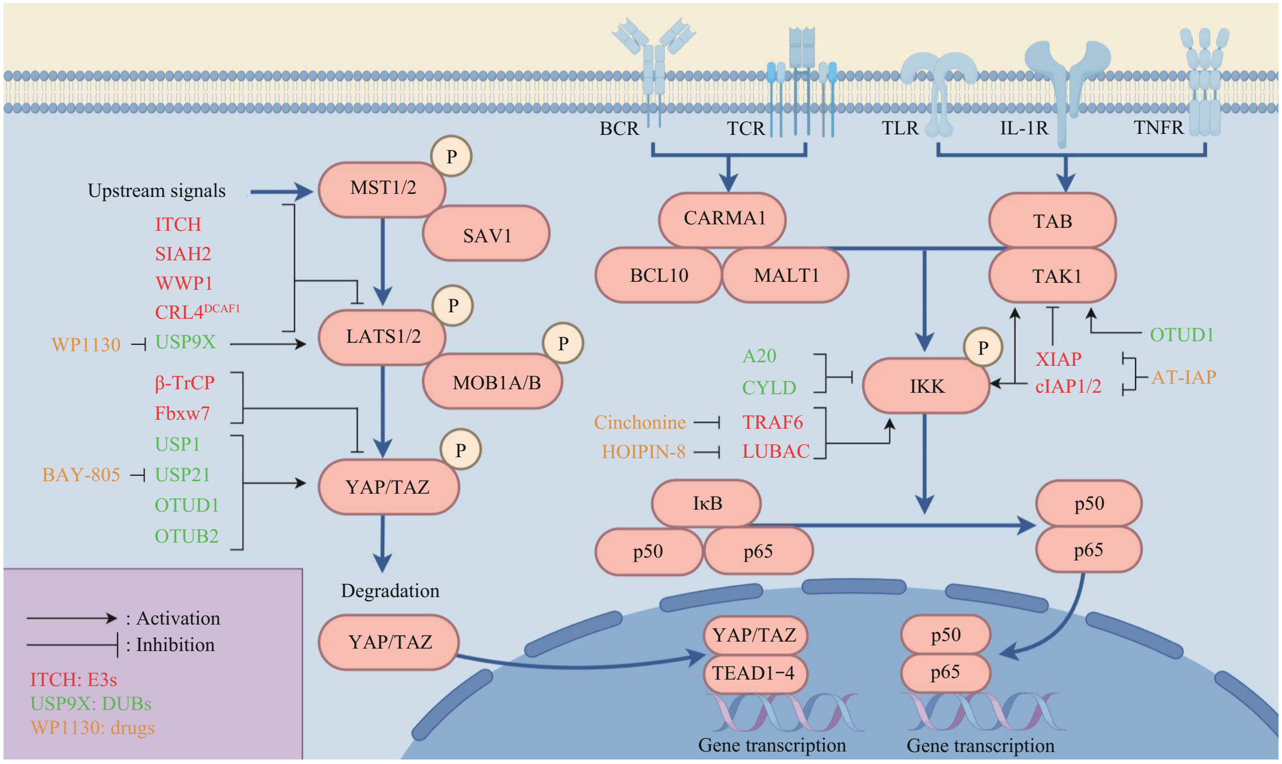


Fig. 2　The Hippo and canonical NF-κB pathways and their current models of regulation by E3s and DUBs (by Figdraw)

When the Hippo pathway is activated, MST1/2 and its scaffold protein SAV1 phosphorylate LATS1/2 and its scaffold MOB1A/B. Phosphorylated MOB1A/B further induces conformational changes in LATS1/2, activating LATS1/2. Activated LATS1/2 phosphorylates and inhibits YAP/TAZ, preventing its nuclear translocation. When the Hippo pathway is inactive, YAP/TAZ translocate to the nucleus, binds to the transcription factor TEAD1-4, induces gene expression, and regulates cell proliferation, apoptosis, and stem cell self-renewal. The figure also illustrates the regulation of the Hippo pathway by E3s and DUBs, as well as the modulation of this pathway by certain drugs targeting E3s and DUBs. BCR and TCR initiate multi-stage enzymatic reactions to activate the CARMA1/BCL-10/MALT1 complex. TLR, IL-1R, and TNFR mainly promote activation of the TAK1/TAB complex. The activated CARMA1/BCL-10/MALT1 and TAK1/TAB complexes phosphorylate the IKK complex. IKK induces phosphorylation of IκB molecules, promoting their ubiquitination and degradation. This releases p65/p50, which, as a transcription factor, activates target gene transcription, thereby promoting tumor development. The figure also illustrates the regulation of canonical NF-κB pathway by E3s and DUBs, as well as the modulation of this pathway by certain drugs targeting E3s and DUBs.

2　Targeting E3s and DUBs to modulate abnormal pathways

As mentioned above, we have introduced four signaling pathways closely related to OSCC and the E3s and DUBs associated with these pathways. We found that gain-of-function or loss-of-function mutations in the components of these pathways or in the ubiquitinases can lead to the occurrence and development of OSCC. Therefore, targeting these pathways' molecules is an interesting therapeutic direction for OSCC. Many reviews have covered drugs directly targeting these pathway components. For instance, Davoodi-Moghaddam *et al*.[167] reviewed drugs targeting the PI3K/AKT/mTOR pathway; de Pellegars-Malhortie *et al.*[168] covered those targeting the Wnt/β-catenin pathway; Li *et al.*[169] focused on the Hippo pathway; and Guo *et al.*[117] introduced drugs targeting the NF-κB pathway. So, we focus on ubiquitination-related targeted therapeutics.

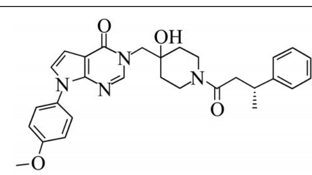
Through hydrophobic interactions and hydrogen bonds[170], YCH2823 inhibits the deubiquitinating function of USP7 by binding to its catalytic domain. Meanwhile, YCH2823 exhibits significant synergistic effects when used in combination with mTOR inhibitors, suggesting that it may enhance antitumor activity through cross-regulatory networks[171]. Mitoxantrone has been confirmed as an inhibitor of USP11, directly binding to and inhibiting the deubiquitinating activity of USP11[172]. In the PI3K/AKT/mTOR pathway, Mitoxantrone can also directly bind to AKT and exert an inhibitory effect, thereby inhibiting the PI3K/AKT/mTOR pathway[173]. Mitoxantrone has already been approved by the U.S. Food and Drug Administration (FDA) for the treatment of multiple sclerosis (MS) and cancer[174-175].

In addition, some drug molecules can target multiple E3s and DUBs. AT-IAP is a novel, potent, dual-target therapies. As stated earlier, ubiquitination and deubiquitination are two major post-transcriptional regulation methods, affecting the stability and activity of signaling pathways. Antagonists or agonists of E3s and DUBs related to these pathways may be significant for OSCC treatment. Relevant drugs are listed in Table 2, and their specific relevance to related pathways can be seen in Figure 1, 2.

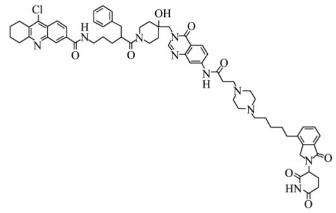
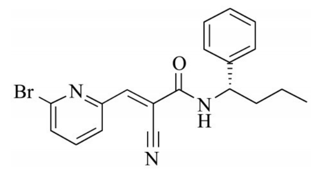
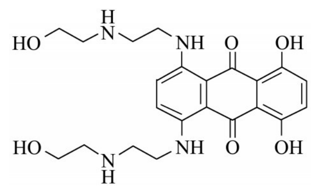
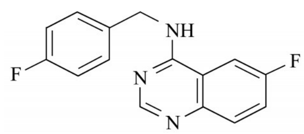
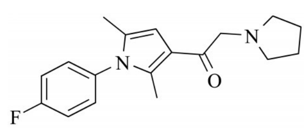
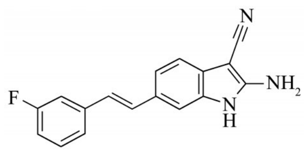
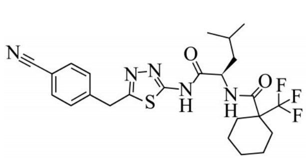
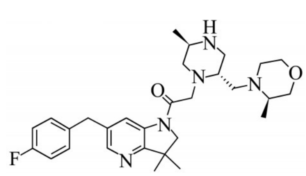
In the preceding sections, we have listed the relevant E3s and DUBs for each signaling pathway. It can be observed that some E3s and DUBs can exert regulatory effects in different signaling pathways, such as USP7 and USP11. Therefore, targeting these E3s and DUBs may have significant therapeutic effects for OSCC. YCH2823 belongs to the second generation of USP7 inhibitors. Compared to the first generation, the activity of the second generation of USP7 inhibitors has been significantly improved, with an IC_{50} reaching the nanomolar level, while the first generation is mostly in the micromolar range[176]. YCH2823 is derived from the structural optimization of the lead compound FT671 through a "scaffold hopping" strategy. Its molecular design targets key residues in the catalytic pocket of USP7, such as V296, Q297, F409, Y465, and Y514, enhancing binding affinity and selectivity. It is a small-molecule dual inhibitor with oral bioactivity that can simultaneously target cIAP1 and XIAP of the IAP family[177]. As a dual inhibitor, AT-IAP mimics endogenous IAP antagonists, binding to the BIR domain of IAP proteins to restore apoptosis in cancer cells[178]. Kunimasa *et al*.[179] found that spautin-1 is an inhibitor of USP10 and USP13 that can increase the apoptosis sensitivity of cancer cells under glucose starvation.

However, traditional small-molecule drugs have limitations such as insufficient targeting when treating diseases. To improve drug development, a new technology called proteolysis-targeting chimera (PROTAC) is emerging. The concept of PROTAC was first proposed by the Crews team in 2001. PROTAC molecules typically consist of 3 parts: a ligand that binds to the target protein, a ligand that binds to an E3 ligase, and a linker that connects the two[180]. One end of the PROTAC molecule binds to the protein of interest (POI), while the other end recruits the E3 ligase. By inducing the ubiquitination of the POI, it marks the POI for degradation by the proteasome[181]. Studies have reported a PROTAC called PU7-1, which can rapidly and specifically degrade USP7 at low nanomolar concentrations and has shown significant anticancer effects in triple-negative breast cancer (TNBC) cells[182]. Compared to traditional small-molecule inhibitor, PROTAC only need to bind to the surface of the POI, not its active center; they directly degrade the POI instead of inhibiting its function[183]. The better targeting and ability to overcome drug resistance make PROTACs more favorable than traditional inhibitors. Additionally, PROTAC can produce longer-lasting biological effects[184]. Therefore, PROTAC technology has great potential in developing new, specific targeted anticancer drugs. In 2019, the first PROTAC molecules entered clinical trials, and several PROTAC molecules are now in different stages of clinical trials[185]. It is reasonable to believe that in the future, more efficient PROTAC will be used to treat various cancers, including OSCC.

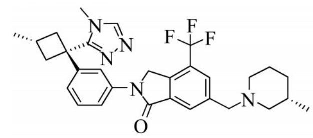
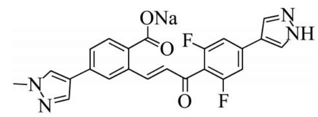
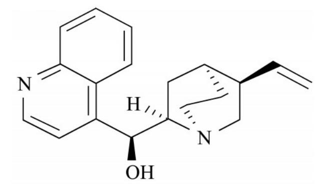
Table 2 Drugs that target E3s and DUBs in OSCC

Pharmaceutical molecules	Targeted protein	Mode of action	Chemical formula	Molecular structure	Reference
YCH2823	USP7	YCH2823 inhibits the deubiquitinating activity of USP7 by binding to its catalytic domain	$C_{29}H_{32}N_4O_4$		[170]

Continued to Table 2

Pharmaceutical molecules	Targeted protein	Mode of action	Chemical formula	Molecular structure	Reference
PU7-1	USP7	PU7-1 promotes the ubiquitination of USP7, leading to its proteasomal degradation	$C_{65}H_{75}ClN_{10}O_8$		[182]
WP1130	USP9X	WP1130 directly binds to the catalytic domain of USP9X, inhibiting its activity	$C_{19}H_{18}BrN_3O$		[186]
Mitoxantrone	USP11	Mitoxantrone directly binds and inhibits the deubiquitinating activity of USP11	$C_{22}H_{28}N_4O_6$		[172]
Spautin-1	USP10/ USP13	Spautin-1 inhibits the activity of USP10 and USP13 by binding to their catalytic domains	$C_{15}H_{11}F_2N_3$		[187]
IU1	USP14	IU1 exerts its inhibitory effect by binding to the catalytic domain of USP14	$C_{18}H_{21}FN_2O$		[188]
GSK2643943A	USP20	GSK2643943A can inhibit the activity of USP20, and the specific mechanism is unknown	$C_{17}H_{12}FN_3$		[189]
BAY-805	USP21	BAY-805 inhibits the activity of USP21 by binding to its catalytic domain	$C_{24}H_{28}F_3N_5O_2S$		[190]
AT-IAP	cIAP1/ XIAP	AT-IAP binds to the BIR domain of IAP proteins, exerting an inhibitory effect	$C_{29}H_{40}FN_5O_2$		[178]

Continued to Table 2

Pharmaceutical molecules	Targeted protein	Mode of action	Chemical formula	Molecular structure	Reference
NX-1607	Cbl-b	NX-1607 inhibits the opening of the LHR and RING domains of Cbl-b, preventing it from binding to E2 ubiquitin enzyme	$C_{30}H_{34}F_3N_5O$		［191］
HOIPIN-8	LUBAC	HOIPIN-8 inhibits LUBAC activity by targeting the HOIP subunit	$C_{23}H_{15}F_2N_4NaO_3$		［192］
Cinchonine	TRAF6	Cinchonine inhibits TRAF6 activity by binding to its RING domain	$C_{19}H_{22}N_2O$		［193］

3 Conclusion and perspective

In this review, we summarize 4 aberrant signaling pathways in OSCC, the regulation of these pathways by ubiquitination/deubiquitination, and drugs targeting E3s and deubiquitinating enzymes. OSCC, one of the most common malignancies globally, is highly complex at genetic and epigenetic levels. Its development is closely related to abnormal activation of multiple signaling pathways, which often manifests as overexpression/activating mutations or deletions/inactivating mutations in pathway components. Recently, sequencing of 176 OSCC patients revealed that the most frequently mutated genes were *TP53* and *CDKN2A*[194]. *TP53* mutations are present in 60%−80% of oral squamous cell carcinomas[195]. These mutations mainly affect the p53 canonical signaling pathway, leading to the loss of cell cycle arrest and apoptosis functions. Mutant p53 can inhibit the activity of wild-type p53, thereby disrupting DNA damage repair and genomic stability[196-197]. Notably, *TP53* mutations can also impact the Wnt/β-catenin pathway. *TP53* mutations have been proven to be associated with β-catenin nuclear translocation, with mutant p53 forming a complex with β-catenin to activate Wnt target genes and exert oncogenic effects[198]. Additionally, *NOTCH1* mutations were identified in whole-exome sequencing of 168 OSCC samples in another cohort, primarily affecting the NOTCH pathway[199]. *NOTCH1* mutations directly alter the structure or function of NOTCH receptor, impacting its ligand binding, proteolytic cleavage, or nuclear translocation processes, thereby abnormally regulating the transcription of downstream target genes[200]. Additionally, *NOTCH1* mutations can activate the NOTCH1/HES1 pathway to inhibit PTEN expression, thereby indirectly activating the PI3K/AKT/mTOR pathway[201-202]. *NOTCH1* deletion mutations can also lead to abnormal expression of downstream target genes, relieve the suppression of TAZ, thereby inhibiting the Hippo pathway and promoting tumorigenesis[203-204]. Moreover, amplification of the q22−q29 region of chromosome 3 is a significant feature of OSCC[205]. This region mainly includes the following cancer-related genes: *CLDN16* (3q29), *SCRIB* (3q29), *IKBKB* (3q22.3), *PIK3CB* (3q28), *TP63* (3q28), *SOX2* (3q26.3), *IGF2BP2* (3q27.2), *RNF13* (3q26.1), *DHX36* (3q22.1), *OPA1* (3q29), *SENP2* (3q29) [206-208]. Among these, *IKBKB* encodes IKKβ, and its amplification can lead to the continuous activation of the NF-κB pathway, promoting tumor growth and survival; *PIK3CB* encodes the catalytic subunit of PI3K, which is involved in the PI3K/AKT/mTOR signaling pathway[209-211]. It can be seen that abnormal activation of signaling pathways plays an important role in the occurrence and development of OSCC. Therefore, research on abnormal signaling pathways is necessary and promising.

Meanwhile, post-translational modifications, especially ubiquitination and deubiquitination, are being increasingly revealed by research. E3s and DUBs can specifically regulate the activity and stability of substrate proteins through their enzymatic activities, thereby regulating related signaling pathways. This is crucial for the occurrence, development, and therapeutic sensitivity of OSCC. For example, the PI3K/AKT/mTOR pathway, one of the most frequently mutated pathways in OSCC, is abnormally activated in about 70% of OSCC cases[212]. Among the abnormal components of PI3K/AKT/mTOR pathway, the most common are overexpression/activating mutations of PI3K subunits and AKT, and deletion or inactivating mutations of PTEN[213-215]. Studying E3s and DUBs targeting these components and their interconnections is of great significance for exploring the molecular mechanisms of OSCC occurrence and developing targeted drugs. Among the E3s and DUBs mentioned above, USP14 has already demonstrated a promoting effect on OSCC in animal models. Chen *et al*.[216] used an oral squamous cell carcinoma xenograft mouse model and found that knockout of *USP14* or the use of USP14 inhibitors could significantly inhibit tumor growth and promote cancer cell apoptosis. Some E3s and DUBs, such as USP7, USP9X, c-Cbl and CYLD, have exhibited their roles in the occurrence and development of other tumors in animal models[217]. However, the majority of E3s and DUBs are still in the basic research stage at present, showing promising targets for OSCC.

Given the significant role of the ubiquitin system in regulating signaling pathways, drug research targeting this system is of great significance for OSCC treatment. Due to the specificity of E3s and DUBs, more and more targeted drugs are being developed. Compared with traditional proteasome inhibitors, these drugs usually show higher precision and fewer side effects[218]. Taking NX-1607 as an example, it is a Cbl-b inhibitor. Cbl-b, as an E3 ligase, can mediate the ubiquitination and degradation of β-catenin, thereby regulating the function of the Wnt/β-catenin pathway. NX-1607 interacts with the Y363 site of Cbl-b, preventing the opening of the LHR and RING domains of Cbl-b. These domains are responsible for binding to E2 binding enzymes, thus inhibiting its E3 ligase activity. Currently, NX-1607 is undergoing phase I clinical trials for advanced malignancies, and early clinical results show that it has efficient anti-tumor activity[191].

Due to the limitations of traditional small-molecule drugs, such as insufficient targeting and easy drug resistance, PROTAC technology has received increasing attention in recent years. PROTAC molecules can simultaneously bind POI and E3s, promoting the ubiquitination of POI. However, only some PROTAC molecules target E3s and DUBs, and research on PROTAC related to OSCC is still limited. For example, the previously mentioned PU7-1 can rapidly and specifically degrade USP7 at low nanomolar concentrations. USP7 promotes cancer by regulating the PI3K/AKT/mTOR pathway. Can PU7-1 be used to treat OSCC? Can we use PROTAC technology to develop more drugs targeting E3s and DUBs? Perhaps these drugs not only have the characteristics of high precision and low side effects of E3s/DUBs targeted drugs, but also have the advantages of good targeting and low drug resistance of PROTAC drugs. This is a very interesting direction for researching therapeutic drugs for OSCC.

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口腔鳞状细胞癌中的泛素化和去泛素化：潜在的药物靶点*

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摘要　口腔鳞状细胞癌（OSCC）是全球最常见的头颈部恶性肿瘤之一，占所有口腔癌的90%以上，具有高度侵袭性和长期预后差等特点。其发病与吸烟、饮酒及人乳头瘤病毒感染等多因素相关。癌前病变主要为口腔黏膜白斑和红斑，其中又以口腔黏膜白斑最为常见。无论是OSCC还是癌前病变，其发生和发展都与多条信号通路的异常激活密切相关。翻译后修饰（如泛素化和去泛素化）通过调节蛋白质的稳定性和活性，在信号通路的调控中发挥关键作用。越来越多的证据表明，异常的泛素化/去泛素化修饰可以通过调控信号通路介导OSCC的发生发展。泛素化/去泛素化过程主要包括泛素连接酶（E3s）对底物的泛素化修饰，去泛素化酶（DUBs）对泛素链的去除和26S蛋白酶体复合物对泛素化底物的降解。E3s和DUBs的异常表达或突变可导致关键肿瘤相关蛋白质稳定性异常，进而驱动OSCC的发生发展。因此，了解OSCC中异常激活的信号通路以及通路中泛素化/去泛素化的调控机制，有助于揭示OSCC的潜在分子机制，并通过靶向相关组分来改善OSCC的治疗。本文总结了PI3K/AKT/mTOR通路、Wnt/β-catenin通路、Hippo通路和经典NF-κB通路这4条在OSCC中异常的信号通路，系统梳理了泛素化/去泛素化在其中的调控机制及潜在药物靶点。PI3K/AKT/mTOR通路在约70%的OSCC中异常激活。PI3K/AKT/mTOR通路在约70%的OSCC中异常激活，该通路受E3s（如FBXW7、NEED4）和DUBs（如USP7、USP10）调控：FBXW7、USP10抑制通路中的信号传递，NEDD4、USP7促进信号传递。Wnt/β-catenin通路异常激活导致β-catenin发生核转位并诱导细胞增殖，该通路受E3s（如c-Cbl、RNF43）和DUBs（如USP9X、USP20）调控：c-Cbl、RNF43抑制通路中的信号传递，USP9X、USP20促进信号传递。Hippo通路失活使YAP/TAZ发生核转位并促进癌细胞转移，该通路受E3s（如$CRL4^{DCAF1}$、SIAH2）和DUBs（如USP1、USP21）调控：$CRL4^{DCAF1}$、SIAH2抑制通路中的信号传递，USP1、USP21促进信号传递。经典NF-κB通路持续激活与炎症微环境及化疗耐药相关，该通路受E3s（如TRAF6、LUBAC）和DUBs（如A20、CYLD）调控：A20、CYLD抑制通路中的信号传递，TRAF6、LUBAC促进信号传递。靶向这些E3s和DUBs为OSCC的药物研究提供了方向。小分子抑制剂如USP7抑制剂YCH2823、USP20抑制剂GSK2643943A及LUBAC抑制剂HOIPIN-8已在临床前模型中显示良好抗肿瘤活性；PROTAC分子通过结合靶蛋白表面位点并招募E3酶，实现了对小分子抑制剂不敏感蛋白的靶向泛素化降解，如PU7-1介导USP7降解，为突破传统药物瓶颈提供新思路。目前，Cbl-b抑制剂NX-1607已进入I期临床试验，初步结果证实其安全性及抗肿瘤活性。未来，研究OSCC中异常的E3s和DUBs，进而研制特异性抑制剂，对于OSCC的精准治疗具有重要意义。

关键词　口腔鳞状细胞癌，泛素化，去泛素化，药物靶点
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