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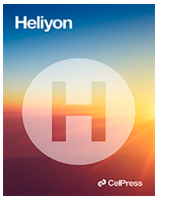

Review article

Ubiquitin-modifying enzymes in thyroid cancer : Mechanisms and functions

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ABSTRACT

Thyroid cancer is the most common malignant tumor of the endocrine system, and evidence suggests that post-translational modifications (PTMs) and epigenetic alterations play an important role in its development. Recently, there has been increasing evidence linking dysregulation of ubiquitinating enzymes and deubiquitinases with thyroid cancer. This review aims to summarize our current understanding of the role of ubiquitination-modifying enzymes in thyroid cancer, including their regulation of oncogenic pathways and oncogenic proteins. The role of ubiquitination-modifying enzymes in thyroid cancer development and progression requires further study, which will provide new insights into thyroid cancer prevention, treatment and the development of novel agents.

1. Introduction

Thyroid cancer is the most common tumor of the endocrine system, representing 3.0 % and 0.4 % of the total global incidence and mortality of thyroid cancer in 2020, respectively. The incidence of advanced thyroid cancer and thyroid cancer-related deaths continues to increase [1]. Various risk factors contribute to the development of thyroid cancer, including chromosomal and genetic alterations, iodine intake, thyroid stimulating hormone (TSH) levels, autoimmune thyroid disease, gender, estrogen, obesity, lifestyle changes, and environmental pollutants [2–5]. The fifth edition of the World Trade Organization (WTO) Classification of Endocrine and Neuroendocrine Tumors categorizes thyroid tumors into eight main groups, with follicular cell-derived neoplasms and thyroid C-cell-derived cancer being the most common categories [6]. Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) make up over 90 % of thyroid malignant tumors, falling under differentiated thyroid cancer (DTC). Most patients can be successfully treated with surgery, radioactive iodine therapy, and TSH inhibition therapy, although 20 % may experience local recurrence and 10 % distant metastasis. Iodine-refractory thyroid cancer, a subset with a less than 10 % 10-year survival rate, has a poor prognosis [7–9].

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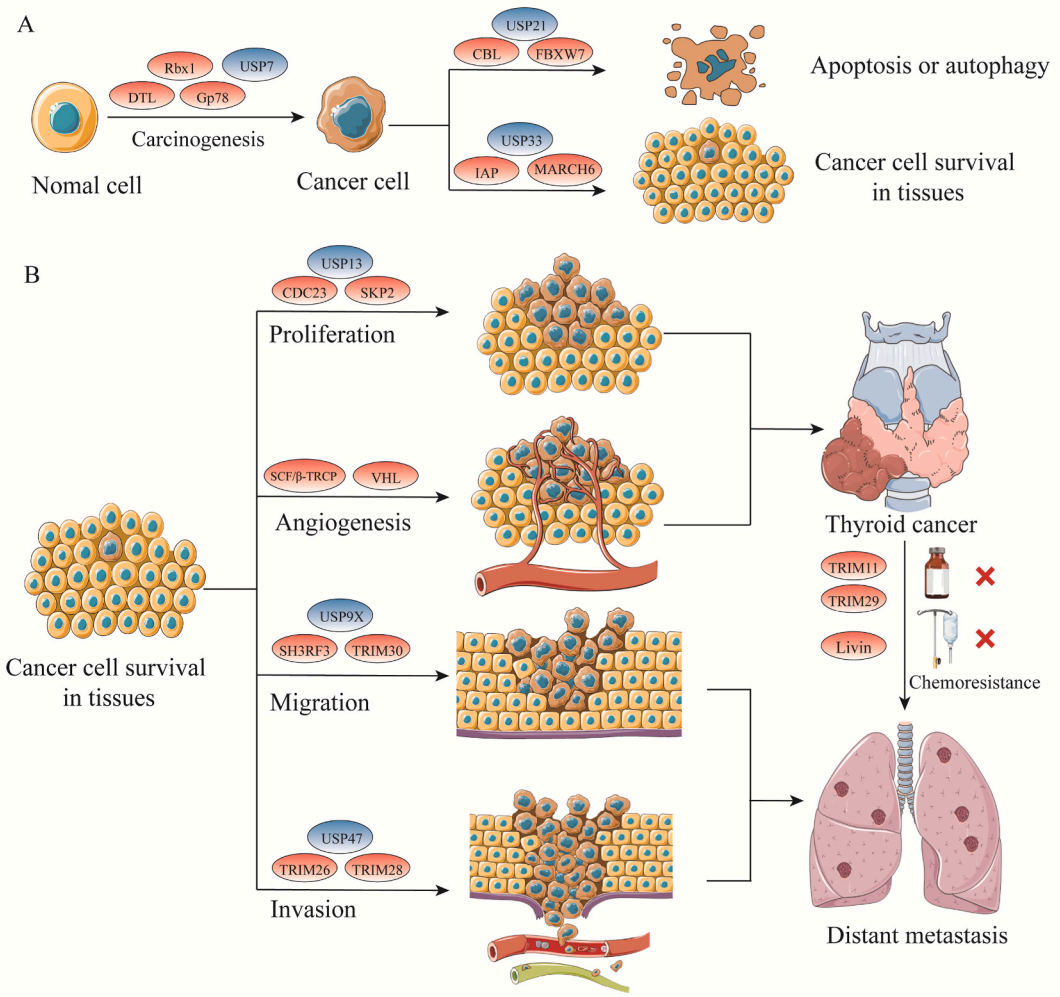

Fig. 1. Ubiquitinating enzymes and DUBs are involved in the development of thyroid cancer. (A) Normal cells become cancer cells under the regulation of ubiquitinating enzymes and DUBs such as Rbx1, USP, DTL, Gp78, etc. Cancer cells will apoptosis or autophagy under the regulation of USP21, CBL, FBXEW7, etc., while USP33, IAP, MARCH6, etc. Protect cancer cell survival in thyroid tissue. (B) Surviving cancer cell has enhanced proliferation and angiogenesis under the regulation of ubiquitinating enzymes and DUBs such as USP13, CDC23, SKP2, SCF/β-TRCP, VHL, etc., which promotes the occurrence and development of thyroid cancer. USP9X, SH3RF3, TRIM30, USP47, TRIM26, and TRIM28 promote cancer cell migration, invasion, and distant metastasis of thyroid cancer. During the treatment of thyroid cancer, TRIM11, TRIM29, Livin, etc. make the tumour cells resistant to chemotherapy and promote further development of thyroid cancer. CBL, Cbl proto-oncogene; CDC23, Cell division cycle 23; DTL, Denticleless E3 Ubiquitin Protein Ligase Homolog; FBXW7, F-box and WD repeat domain containing 7; Gp78, Glucose regulated protein 78 kD; IAP, Inhibitor of apoptosis protein; MARCH6, Membrane-associated RING-CH 6; Rbx1, Ring-Box 1; SCF/β-TRCP, Skp/Cullin1/F-Box protein (β-transducin repeat-containing protein); SH3RF3, SH3 Domain Containing Ring Finger 3; SKP2, S-phase kinase-associated protein 2; TRIM, Tripartite motif; USP, Ubiquitin Specific Proteinase; VHL, von Hippel-Lindau tumor suppressor [Graphing via SMART (https://smart.servier.com/) and Adobe Illustrator].

Anaplastic thyroid cancer (ATC), a rare tumor comprising 1 % of thyroid malignancies, is highly aggressive with a median survival of only 6 months [10]. Medullary thyroid carcinoma (MTC), on the other hand, accounts for 1–2% of thyroid malignancies and is primarily treated with surgery and molecular targeted therapy, as traditional cytotoxic drugs are ineffective [11,12]. At the molecular level, various driver mutations are linked to the malignancy of PTC and its clinicopathologic characteristics. These mutations include point mutations in *BRAF*, *TERT*, or *RAS*, as well as *RET* rearrangements. For FTC, mutations in the *RAS* gene family (*HRAS*, *KRAS*, and *NRAS*) are most common, with *TERT* promoter mutations present in over 10 % of cases. *TERT* promoter mutations and TP53 mutations are frequently observed in ATC, while RET mutations are predominant in MTC [12]. Despite progress in thyroid cancer treatment, numerous challenges remain to be addressed. Further research is essential to enhance our understanding of thyroid cancer development and treat.

Post-translational modification (PTM) is a crucial aspect of epigenetic regulation, encompassing various modifications such as methylation, acetylation, glycosylation, phosphorylation, and others. PTM is a dynamic and reversible process that involves the

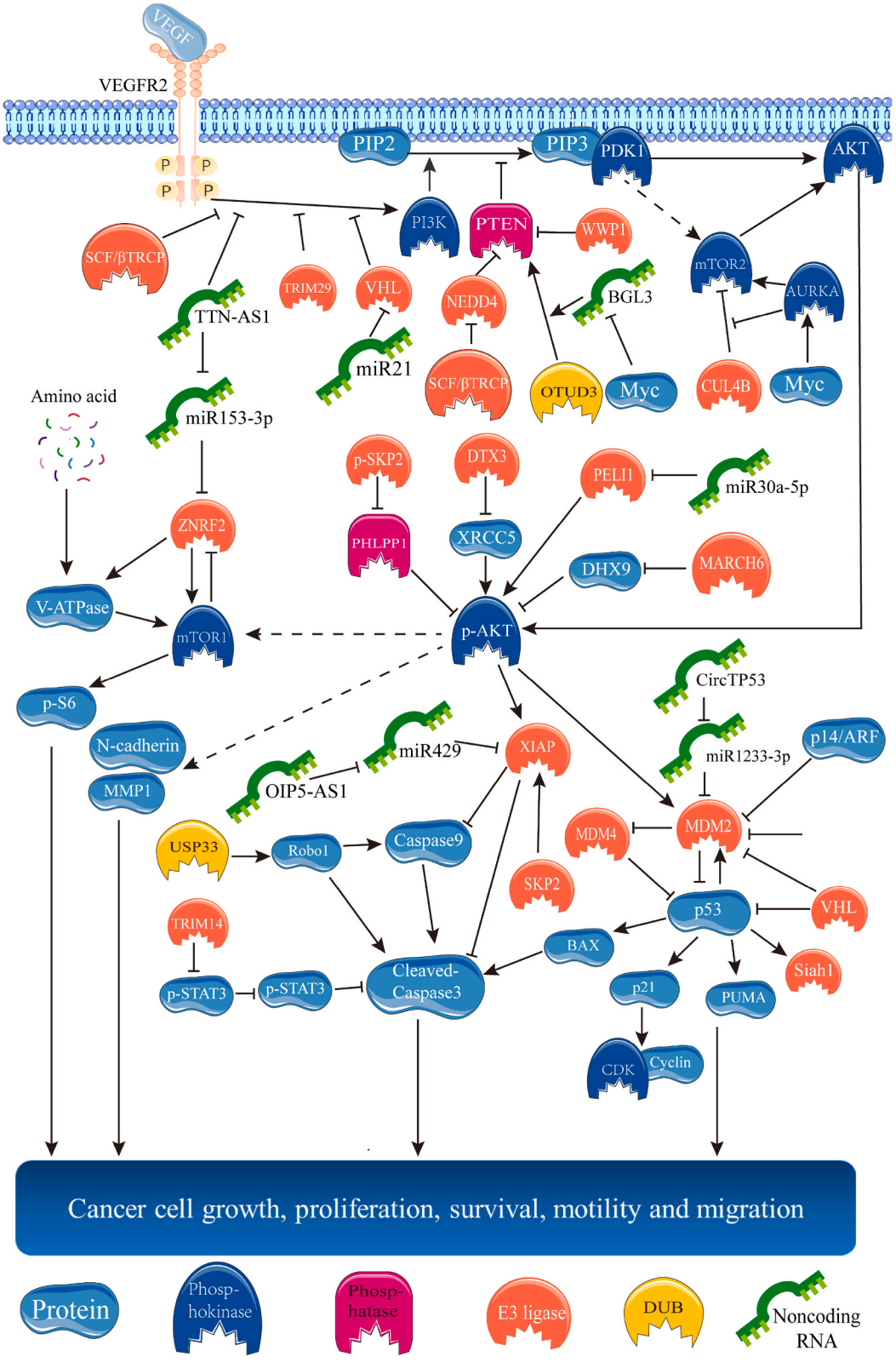

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Fig. 2. In DTC, E3 ubiquitin ligases and DUBs are involved in regulating the AKT pathway. Solid arrows indicate activation and flat arrows indicate inhibition. RTKs represented by VEGFR bind to ligands such as VEGF, which leads to the activation of its downstream PI3K/AKT pathway and enhances DTC growth, proliferation, survival, invasion, and migration. E3 ubiquitin ligases and DUBs are involved in the regulation of the activity or expression levels of several proteins in the AKT signaling pathway, and their dysregulation is an important cause of DTC occurrence and development. AKT, Rac-Alpha Serine/Threonine-Protein Kinase; AURKA, Aurora Kinase A; BAX, BCL2-Associated X; CDK, Cyclin-dependent kinase; CUL4B, Cullin4B; DHX9, DExH-box helicase 9; DTX3, Deltex E3 Ubiquitin Ligase 3; HUWE1, HECT, UBA and WWE domain containing E3 ubiquitin protein ligase 1; MARCH6, membrane-associated RING-CH6; MDM2, murine double minute 2; MDM4, murine double minute 4; MMP1, Matrix metalloproteinase-1; mTOR, mammalian target of rapamycin; Myc, MYC proto-oncogene, bHLH transcription factor; NEDD4, neuronally expressed developmentally downregulated 4; OTUD3, OTU domain-containing protein 3; PDK1, 3′-phosphoinositide-dependent kinase 1; PELI1, pellino E3 ubiquitin protein ligase 1; PHLPP1, PH Domain And Leucine Rich Repeat Protein Phosphatase 1; PI3K, Phosphoinositide 3-Kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PTEN, Phosphatase and tensin homolog; PUMA, p53 upregulated modulator of apoptosis; p-S6, Phospho-S6 Ribosomal Protein; Robo1, roundabout guidance receptor 1; SCF/β-TRCP, Skp/Cullin1/F-Box protein (β-transducin repeat-containing protein); Siah1, seven in absentia homolog-1; SKP2, S-phase kinase-associated protein 2; SOCS1, suppressor of cytokine signaling 1; STAT3, signal transducer and activator of transcription 3; TRIM, Tripartite motif; USP33, Ubiquitin Specific Proteinase 33; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor; VHL, von Hippel-Lindau tumor suppressor; WWP1, WW domain-containing E3 ubiquitin protein ligase 1; XIAP, X-linked inhibitor of apoptosis protein; XRCC5, X-ray repair cross complementing 5 Gene; ZNRF2, zinc and ring finger 2 [Graphing via SMART (https://smart.servier.com/) and Adobe Illustrator].

addition of biochemical components to proteins, thereby influencing their structure, localization, and function [13]. Research has shown that PTM plays a critical role in the development of human diseases, including cancer, with dysfunction in PTM observed in various diseases [14–16]. Protein ubiquitination, a specific type of PTM, involves the covalent binding of ubiquitin, a small, conserved protein, to target proteins. This process regulates protein stability, localization, and function, and is involved in essential cellular processes such as metabolism, cell cycle progression, DNA repair, and signal transduction [17–19]. Ubiquitination has been linked to diseases such as inflammation, neurodegenerative disorders, and genetic conditions [20–22]. Studies have demonstrated that modulators of ubiquitination can either promote or inhibit different types of cancers by regulating the ubiquitination levels of specific targets. For instance, ubiquitin-conjugating enzyme E2 J1 (UBE2J1) inhibits the progression of colorectal cancer by promoting the ubiquitination and degradation of Ribosomal protein S3 (RPS3) [23]. Recent evidence has increasingly shown the involvement of ubiquitination in the development of thyroid cancer. This review aims to explore the role of ubiquitination in thyroid cancer (Fig. 1 A&B).

2. Ubiquitination and deubiquitination

Ubiquitin (Ub) is a small protein molecule composed of 76 amino acids and has a molecular weight of around 8.5 kDa. It has remained highly conserved throughout evolutionary history. Ubiquitination is the enzymatic process through which ubiquitin attaches covalently to a target protein [17]. Substrate proteins can undergo modification by single ubiquitin molecules (mono-ubiquitination and multiple mono-ubiquitination) or by chains of ubiquitin molecules (polyubiquitination) [24]. In polyubiquitination chains, ubiquitin can be connected through seven lysine residues (K6, K11, K27, K29, K33, K48, and K63) or through the first methionine (M1), with K48-linked and K63-linked polyubiquitination being the most prevalent forms [25,26]. The various forms of substrate ubiquitination lead to different biological outcomes. Monoubiquitination can enhance protein recognition, facilitate complex formation, and maintain cellular homeostasis. On the other hand, Lys48-linked polyubiquitination marks proteins for proteasomal degradation, whereas Lys63 chains play non-degradative roles in cellular signaling, intracellular transport, DNA damage response, and other cellular processes [25–27].

Multiple enzymes participate in the ubiquitination process, including two E1 enzymes, 38 E2 enzymes, and over 600 E3 enzymes [24,28,29]. In this process, E1 initially binds to ubiquitin in an ATP-dependent manner and then transfers ubiquitin to its cysteine residues [30]. Subsequently, E2 transfers ubiquitin from E1 to its own active site cysteine through a thioester reaction. Finally, the E3 enzyme interacts with both the substrate protein and the E2∼ubiquitin thioester to transfer ubiquitin to the substrate protein's lysine, forming an isopeptide linkage [31]. The specificity of the ubiquitin system is governed by the E3 ligase, which selectively targets proteins for ubiquitination modifications [32]. E3 ligases are categorized into three families: the RING finger family, the HECT family, and the RBR family [33]. RING finger E3s act as ubiquitin transferases, facilitating the transfer of ubiquitin from E2 to the target substrate [34–36]. HECT E3s possess an N-terminal substrate binding domain and a C-terminal HECT domain, while RBR E3s consist of RING1, RING2, and the IBR domain [37,38]. Unlike RING finger E3s, HECT and RBR E3s contain a catalytic cysteine that accepts ubiquitin from E2∼ubiquitin and transfers it to the substrate [39,40].

Deubiquitination is a crucial aspect of protein ubiquitination modification, with deubiquitinases (DUBs) playing a key role in this process. The number and expression of DUBs can vary not only between species but also within different tissues or cells of the same species [41]. In humans, approximately 100 DUBs have been identified and classified into six families [25]. Each DUB contains at least one ubiquitin-binding site, known as the S1 site, which guides the ubiquitin C terminus to the active site for hydrolysis and subsequent removal of the ubiquitin or ubiquitin chain from the substrate [42].

3. Differentiated thyroid cancer

In normal cells, protein ubiquitination and deubiquitination are tightly regulated to maintain protein homeostasis. However, this

balance is disrupted in cancer cells. Dysregulation of ubiquitination modification leads to abnormal activation or blockage of multiple pathways, resulting in uncontrolled cell proliferation, apoptosis, invasion, migration, and other activities. Ubiquitination plays a crucial role in the development of DTC and is intricately involved in the regulation of multiple pathways, which will be further explored.

3.1. PI3K/AKT pathway

Dysregulation of the PI3K/AKT pathway plays an important role in the development of PTC (Fig. 2). In PTC, E3 ligase $SCF^{\beta-TRCP}$ was found to ubiquitinate the casein kinase 1 δ (CKIδ) phosphorylated vascular endothelial growth factor receptor (VEGFR2) with VEGFA precursors, thereby reducing the *p*-AKT expression and inhibiting peripheral endothelial cell migration and angiogenesis [43]. Upon activation of Receptor tyrosine kinases (RTKs), PI3K will be activated, in which E3 ligase tripartite motif containing 29 (TRIM29) will promote PI3K phosphorylation, leading to enhanced proliferation, invasion, migration, and anti-apoptosis of cancer cells, while E3 ligase TRIM26 can inhibit PI3K phosphorylation and miRNA21 can inhibit PI3K phosphorylation by inhibiting E3 ligase von Hippel-Lindau tumor suppressor (VHL) [44–46]. PI3K is activated to phosphorylate PIP2 phosphorylation to PIP3, and phosphatase and tensin homolog (PTEN) can reverse this process. Knockdown of WW domain-containing E3 ubiquitin protein ligase (*WWP1*) in PTC can upregulate PTEN levels [47]. The E3 ligase neuronally expressed developmentally downregulated 4 (NEDD4) belongs to the same NEDD4 family as WWP1, and in previous experiments, it down-regulated PTEN under the regulation of $SCF^{\beta-TRCP}$. However, in a recent study, it was found that the expression of NEDD4 was reduced in thyroid cancer, which seems to contradict its oncogenic effect, and therefore more studies are needed to prove the role of NEDD4 in thyroid cancer [48,49]. Unlike E3 ligase ubiquitination which degrades PTEN, DUB OTUD3 promotes PTEN deubiquitination and long non-coding RNA (lncRNA) BGL3 can bind PTEN and enhance the deubiquitination of OTUD3, but this process is inhibited by MYC [50].

PIP3 recruits and activates PKD1, indirectly activating mTOR2. In PTC, high expression of *AURKA*, regulated by c-Myc, interacts with SIN1, a subunit of mTOR2, preventing SIN1 ubiquitination by E3 ligase CUL4B and degradation [51,52]. Activated PKD1 and mTOR2 phosphorylate AKT, maintaining its activation in the cytoplasm. AKT phosphorylation is also modulated by various ubiquitinating enzymes. The gene *DHX9* (DExH-box helicase 9), a member of the DExH-box helicase family, unravels DNA and RNA structures [53]. High level of the E3 ligase membrane-associated RING-CH 6 (MARCH 6) in most PTCs destabilizes DHX9, activating the AKT/mTOR pathway, reversible by DHX9 silencing [54]. In a separate investigation, researchers discovered that the E3 ligase S-phase kinase-associated protein 2 (*SKP2*) is overexpressed in papillary thyroid carcinoma (PTC). This overexpression leads to increased AKT phosphorylation by ubiquitinating PH domain leucine-rich repeat protein phosphatase-1 (PHLPP1). Activated AKT, in turn, can phosphorylate SKP2, enhancing its enzymatic activity and promoting its cytoplasmic localization [55]. Additionally, Pellino E3 ubiquitin protein ligase 1 (PELI1) was found to be upregulated in human PTC tissues and cells, a process that is negatively regulated by miR-30c-5p. Cells overexpressing *PELI1* showed elevated levels of P-AKT, as well as increased expression of downstream effectors of the PI3K-AKT signaling pathway, such as Ki-67 and matrix metalloproteinase (MMP2). These proteins are associated with cell proliferation and migration [56]. Deltex E3 ubiquitin ligase 3 (DTX3) is also closely related to AKT phosphorylation, and it has been shown that DTX3 promotes X-ray repair cross complementing 5 (XRCC5) ubiquitination and thus inhibits AKT activation, thereby inhibiting epithelial–mesenchymal transition (EMT) in PTC [57]. A recent study identified GSG2, also known as Histone H3 associated protein kinase (Haspin), as being upregulated in PTC. GSG2 binds to and inhibits SMAD specific E3 ubiquitin Protein Ligase 1 (SMURF1), which prevents the ubiquitinated degradation of Aurora Kinase B (AURKB), resulting in increased levels of AKT phosphorylation [58]. Furthermore, the E3 ligase RAS guanyl releasing protein 3 (RasGRP3) was found to be upregulated in PTC tissues and cell lines. RasGRP3 promotes the activation of murine double minute 2 (MDM2) through AKT phosphorylation [59].

MDM2 is an important E3 ligase among *p*-AKT downstream substances, and high level of MDM2 has been demonstrated in several studies in DTC, which can ubiquitinate and degrade P53, leading to normal cell carcinogenesis [60–62]. MDM4 is structurally similar to MDM2 and in the study of Prodosmo et al. MDM4 mRNA in PTC with wild-type of P53 was significantly downregulated in tumor tissues and further down-regulated with tumor progression, and its expression trend was opposite to that of MDM2 [63]. Whereas, lowering MdM4 levels increased the survival of mice expressing wild-type p53 in the study by Fang et al. [64]. HECT, UBA and WWE domain containing E3 ubiquitin protein ligase 1 (HUWE1), another E3 ligase that can affect MDM2, can protect p53 from degradation and inhibit tumorigenic development by downregulating MDM2 [65]. In addition, the E3 ligase VHL can also act as a positive regulator of the tumor suppressor P53 by inhibiting MDM2-mediated ubiquitination and subsequent recruitment of p53 modifying enzymes [66]. Although there is also evidence that VHL negatively regulates p53 activity by controlling the formation of p53 tetramers and reducing p53 binding at target gene promoters [67]. In addition, CircTP53 is highly level in thyroid cancer and CircTP53 can act as a target of miR-1233-3p to increase MDM2 mRNA levels [68]. $P14^{ARF}$ can also inhibit MDM2 and upregulate *TP53* expression [60]. Additional experiments have shown that stabilizing p53 can also feedback increase MDM2 expression [69,70]. In DTC, P53 dysregulation can dysregulate the expression of oncogenes such as *CDKN1A*, bcl2 associated X (*BAX*), and bcl2 binding component 3 (*BBC3*), resulting in cell cycle dysregulation and decreased apoptosis [70].

In addition to MDM2, activated AKT can also promote cellular carcinogenesis through the activation of mTORC1. In one study, long non-coding RNATTN-AS1 was found to positively regulate not only the protein levels of p-PI3K, *p*-Akt, and *p*-mTORC1 in PTC, but also the expression of the E3 ligase zinc and ring finger (*ZNRF2*), via miR-153-3p, whereas in another study, ZNRF2 could enhance mTORC1 activity via V-ATPase and could be phosphorylated by mTORC1, and the phosphorylated ZNRF2 had a negative feedback regulation on mTORC1 [71,72].

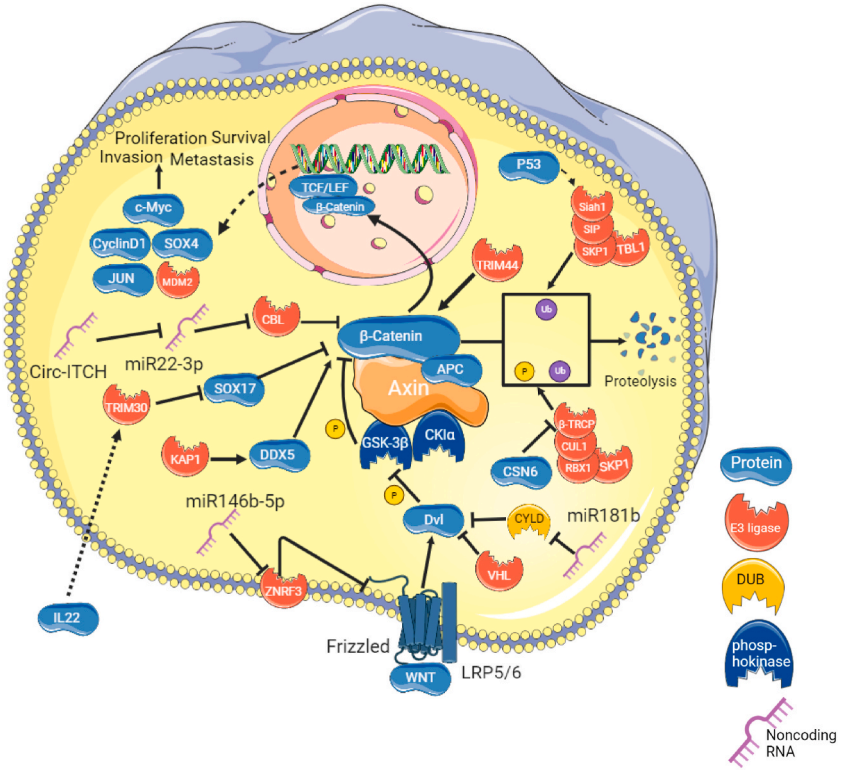

Fig. 3. In DTC, E3 ubiquitin ligases and DUBs are involved in the regulation of the Wnt/β-Catenin pathway. Wnt binds to LRP5/6 and activates Dvl, resulting in the inhibition of GSK-3β activity, and the inability of β-Catenin to be degraded by phosphorylation and non-phosphorylation pathway ubiquitination in the destruction complex. β-Catenin is elevated in the cytoplasm and translocates into the nucleus where it binds to the transcriptional activator TCF/LEF, upregulates target genes, and ultimately strengthens the ability of DTC to proliferate, survive, invade, and migrate. β-TRCP, β-transducin repeat-containing protein; APC, Adenomatous polyposis coli protein; Axin, Axis inhibition protein; CKIα, casein kinase Iα; c-Myc, cellular-myelocytomatosis viral oncogene; CSN6, The COP9 signalosome subunit 6; CUL1, Cullin 1; CYLD, Cylindromatosis; DDX5, DEAD-Box Helicase 5; Dvl, Dishevelled; GSK-3β, glycogen synthase kinase-3β; IL22, Interleukin-22; KAP1, KRAB-associated protein 1; LRP5/6, lipoprotein receptor-related proteins 5 and 6; Rbx1, Ring-Box 1; Siah1, seven in absentia homolog 1; SIP, Siah-1-interacting protein; SKP1, S-phase kinase associated protein 1; SOX4, SRY-box transcription factor 4; SOX17, sex-determining region Y-box; TBL1, transducin β-like protein 1; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; TRIM, Tripartite motif; VHL, von Hippel-Lindau tumor suppressor; ZNRF3, zinc and ring finger 3 [Graphing via SMART (https://smart.servier.com/) and Adobe Illustrator].

3.2. *Wnt/β-catenin pathway*

Ubiquitination modifications are crucial in the Wnt/β-catenin pathway, and their dysregulation plays a significant role in the development of DTC (Fig. 3). In PTC and lymph node metastases, MiR-146b-5p is upregulated, leading to the downregulation of the E3 ligase ZNRF3. ZNRF3 has the ability to interact with Frizzled (FZD) and Lipoprotein receptor-related proteins 5 and 6 (LRP 5/6) complexes, resulting in the ubiquitination and degradation of heterodimeric receptors. This, in turn, inhibits Wnt-driven signaling [73, 74]. When Wnt interacts with FZD at the membrane, it activates downstream Dishevelled (Dvl) through phosphorylation modifications. Dvl then phosphorylates GSK3β, disrupting the degradation complex. During this process, several ubiquitinating enzymes can regulate Dvl, affecting pathway activation. Furthermore, the expression of *VHL* and DUB Cylindromatosis (*CYLD*) is reduced in PTC. Previous studies have shown that VHL can autophagically degrade Dvl through ubiquitination modification, while CYLD specifically deubiquitinates Dvl through k63, decreasing its stability [75–78].

In the degradation complex, glycogen synthase kinase 3β (GSK3β), β-catenin, adenomatous polyposis coli protein (APC), and axis inhibition protein (Axin) are all involved. Under normal conditions, Axin acts as the backbone of the complex, while GSK3β phosphorylates β-catenin with the help of APC. The phosphorylated β-catenin is then recognized by E3 ligase β-TRCP for ubiquitination and degradation. However, in the case of carcinogenesis, GSK3β is phosphorylated and its activity is reduced. This leads to the release of β-catenin from the degradation complex, causing its accumulation in the cytoplasm. The accumulated β-catenin then enters the nucleus to regulate the activity of transcription factors, promoting cancer cell proliferation, invasion, and migration [79]. Therefore, the presence of β-catenin plays a crucial role in the Wnt pathway.

In studies on DTC, two ubiquitinated degradation pathways of β-catenin have been identified: degradation after phosphorylation modification and degradation in the absence of phosphorylation modification. The former pathway was found to be inhibited in PTC. Wen et al. found that elevated the COP9 signalosome subunit 6 (CSN6) in PTC leads to a decrease in β-TRCP level, resulting in reduced

β-catenin degradation and pathway activation [80]. Zhu et al. found that elevated Cadherin 4 (CDH4) in PTC binds β-catenin, thereby interrupting β-catenin-β-TRCP interactions and reducing β-catenin degradation [81]. On the other hand, in FTC, mutation of Thyroid hormone receptor β (TRβ) blocks both degradation pathways simultaneously. In Guigon et al.'s study, TRβ was found to bind to β-catenin, and Triiodothyronine (T3) was found to release β-catenin from TRβ, facilitating its degradation through the APC/GSK3β/β-TRCP or the APC/p53/Siah-1 pathways. However, TRβ mutant TRβ pv blocks the release of β-catenin from TRβ, resulting in its immunity from proteasomal degradation [82].

Furthermore, other ubiquitinating enzymes can also impact the protein levels of β-catenin in cancer cells. Wang et al. and Guo et al. discovered that circ-ITCH, which is lowly expressed in DTC, can upregulate the expression of E3 ligase Cbl proto-oncogene (*CBL*) through its interaction with miR-22-3p. CBL is the E3 ligase responsible for nuclear β-catenin [83,84]. Li et al. demonstrated that IL-22 regulates Sex-determining region Y-box 17 (Sox17) ubiquitination through E3 ligase TRIM30, thereby inducing PTC proliferation [85]. Zhou et al. found that the E3 ligase TRIM44 is high level in human DTC tissues and cell lines. Silencing *TRIM44* significantly downregulates the protein levels of β-catenin, cyclin D1, and c-Myc in DTC [86]. Lan et al. discovered that the expression of E3 ligase KRAB-associated protein 1 (KAP-1) is upregulated in thyroid cancer cells. It positively regulates dead-box helicase 5 (*DDX5*) expression in PTC cells by interacting with DDX5, which, in turn, upregulates β-catenin expression and activates the signaling pathway [87].

3.3. NF-κB patshway

Aberrant Nuclear factor-kappa B (NF-κB) activation is observed in various cancers, including thyroid cancer. It plays a crucial role in tumorigenesis by promoting the expression of anti-apoptotic genes and pro-inflammatory cytokines, ultimately affecting cell survival and tumor progression [88]. Tumor necrosis factor (TNF) receptor-associated factor (TRAF) serves as an E3 ligase in both the classical and non-classical NF-κB pathways. TRAF's involvement in the NF-κB pathway has been observed in thyroid cancers carrying the RET/PTC oncogene. Wixted et al. reported that RET/PTC oncoproteins selectively activate the pro-inflammatory program through TRAF2 and TRAF6. While TRAF-mediated NF-κB pathways may not be necessary in the early stages of carcinogenesis, they likely play a role in the later stages of tumor progression [89]. Neely et al. found that *TRAF3* expression was increased in RET/PTC oncogenes, but its involvement in the activation of the NF-κB pathway was unclear. On the other hand, the level of NF-κB-inducing kinase (NIK), which is degraded downstream by ubiquitination, was also increased [90]. Additionally, several experiments have shown that *TRAF6* expression is reduced in DTC, while TRAF2 can inhibit TNFα-induced cell death [91–93].

Other ubiquitination modifications associated with the NF-κB pathway have been identified in DTC. Yan et al. found that the E3 ligase SMURF1 is high level in PTC cells and promotes the ubiquitination and degradation of kisspeptin 1 (KISS-1). This leads to upregulation of p-p65 and p-i-κBα levels, enhancing the proliferation, migration, and invasive ability of PTC cells [94]. Lan's study revealed that small nucleolar RNA host gene 4 (SNHG4) acts as the competing endogenous RNA (ceRNA) of miR-25. In PTC, downregulation of SNHG4 significantly upregulates miR-25, which subsequently decreases the expression of the E3 ligase F-box and WD repeat domain containing 7 (*FBXW7*). This activation of the NF-κB signaling pathway occurs as a result [95]. Additionally, Li et al. found that overexpression of miR-181b inhibits the DUB CYLD in thyroid cancer. This weakens CYLD's negative regulation in the NF-κB signaling pathway, leading to NF-κB activation and enhanced cell proliferation and colony formation [76].

3.4. Cell cycle pathways

Ubiquitination plays a crucial role in regulating the normal cell cycle [96]. E3 ligase SCF complex and E3 ligase anaphase promoting complex/cyclosome (APC/C) are involved in the degradation of various cyclins and cycle regulatory proteins through ubiquitination, ensuring the proper functioning of the cell cycle. However, in cancer cells, dysregulation of ubiquitination modifications can lead to cell cycle abnormalities, such as in the case of DTC.

In previous studies, ubiquitination has been implicated in the regulation of cycle regulatory proteins, including p21 and p53, in various signaling pathways. Besides, there are also ubiquitinating enzymes that are involved in the expression of cycle regulatory proteins, in addition to their role in signaling pathway regulation. For instance, the expression of E3 ligase *SKP2* and *CDKN1B* showed a negative correlation in thyroid cancer tissues. Differences in SKP2 levels and p27 T187 phosphorylation were found to determine *CDKN1B* expression in thyroid cancer cells and regulate cell proliferation. Overexpression of *SKP2* in thyroid cancer cells cultured in vitro not only promoted cancer cell proliferation but also reduced contact inhibition with low serum-induced G1 blockade [97]. Jun activation domain-binding protein 1 (JAB1), a subunit of the deubiquitinating enzyme COP9 signalosome, was found to be increased in expression in various tumors. In one study, JAB1 expression was significantly elevated in PTC compared to normal thyroid tissue, accompanied by decreased *CDKN1B* expression. Moreover, JAB1 expression was significantly increased in tumor-infiltrating areas and correlated with tumor size [98]. Another report demonstrated that JAB1 was significantly up-regulated in PTC and promoted PTC proliferation and metastasis by up-regulating Angiopoietin-like protein 2 (ANGPTL2) level through deubiquitination [99]. Similarly, DUB Ubiquitin specific proteinase 7 (USP7) was significantly up-regulated in PTC and stabilized T-box transcription factor 3 (TBX3) through deubiquitination, leading to the down-regulation of p57KIP2 level and promoting PTC proliferation [100].

Cell division cycle 23 (CDC23), also known as APC8, is an APC subunit that regulates mitosis by catalyzing the formation of ubiquitin couplings. *CDC23* was found to be overexpressed in PTC & ATC and negatively expressed in normal and proliferative thyroid tissues. Knockdown of *CDC23* in FTC-133 and TPC-1 cells resulted in the accumulation of CyclinB1 and securin, accompanied by an increase in the number of cells in the S- and G2M-phases of the cell cycle. This inhibition of cell proliferation, tumor sphere formation, and anchorage-independent growth was observed [101]. In another study, LINC00514 was found to be up-regulated in both PTC tissues and cell lines and could regulate PTC progression through the LINC00514/miR-204-3p/CDC23 signaling pathway. It enhanced

the proliferation, migration, and invasion of TPC1 cells [102].

Overall, dysregulation of ubiquitination modifications can disrupt the normal cell cycle in cancer cells, as evidenced by the dysregulation of various ubiquitinating enzymes and their target proteins. Understanding the role of ubiquitination in cell cycle regulation and its dysregulation in cancer can provide valuable insights for the development of targeted therapies.

3.5. Apoptosis pathways

Inhibitor of Apoptosis (IAP) is a crucial class of anti-apoptotic factors. It consists of several proteins, such as c-IAP1, c-IAP2, XIAP, ILP2, Livin, etc., which all have a ring domain at their carboxyl terminus [103]. The ring domain of IAP proteins possesses E3 ligase activity, allowing them to mediate protein degradation through the ubiquitin-proteasome pathway [103]. Furthermore, IAP proteins with the ring domain can also facilitate ubiquitination of their own and target proteins, including caspases [104–106].

Numerous studies have demonstrated that XIAP and c-IAP level is upregulated in DTC, leading to the inhibition of apoptosis in cancer cells [107–109]. For instance, Yim et al. discovered that AKT activates XIAP by phosphorylating it and preventing its degradation, thereby inhibiting caspase 3, 7, and 9-mediated apoptosis [110]. Another study by Yu et al. revealed that OIP5-AS1, a long noncoding RNA, is upregulated in PTC tissues and cell lines. OIP5-AS1 acts as a ceRNA to inhibit miR-429, which, in turn, increases the expression of *XIAP* and enhances the proliferation and metastatic ability of PTC cells [111]. Additionally, Werner et al. found that *BIRC5* and *XIAP* are expressed in FTC tissues, while non-tumorigenic thyroid tissues do not exhibit these proteins. Knocking down *BIRC5* and *XIAP* in FTC leads to a significant increase in caspase-3/7 activation [112]. Furthermore, the expression of TNF-related apoptosis-inducing ligand (TRAIL) and its receptor is significantly elevated in FTC tissues compared to non-tumor thyroid tissues. The addition of human recombinant TRAIL induces apoptosis in the FTC cell line but also causes drug resistance. The sensitivity of TRAIL is regulated by IAP family members IAP1 and cIAP2. The addition of Smac mimics degrades cIAP1/2 and enhances TRAIL sensitivity [109].

In addition to IAP proteins, other ubiquitination-associated proteins also play a role in regulating apoptosis in DTC. The E3 ligase TRIM14 is high level in most cases of PTC and is associated with a poor prognosis. Overexpressed *TRIM14* ubiquitinates and degrades suppressor of cytokine signaling 1 (SOCS1), resulting in upregulated p-STAT3 expression. This process does not affect STAT3 expression but decreases Cleaved Caspase 3 and Bax, increases Bcl-2, and inhibits apoptosis in PTC [113]. *SKP2* is overexpressed in a large number of PTC tissues and directly correlates with the overexpression of the anti-apoptotic proteins XIAP and Bcl-xL. Silencing SKP2 significantly increases reactive oxygen species (ROS) production in PTC cells [114]. Moreover, DUB USP33 is downregulated in high-risk PTC patients. Its overexpression activates Caspase 9 and Caspase 3 proteins through Robo1 signaling, promoting apoptosis [115].

In summary, the IAP family of proteins, including XIAP and c-IAP, plays a significant role in inhibiting apoptosis in DTC. Additionally, other ubiquitination-associated proteins, such as TRIM14, SKP2, and USP33, are also involved in apoptosis regulation. Understanding the mechanisms by which these proteins function can provide valuable insights for developing therapeutic strategies to promote apoptosis in DTC.

3.6. Invasion pathways

The treatment outcome for DTC is generally good, but if invasion and metastasis occur, the prognosis of patients becomes significantly worse. Therefore, research on metastatic DTC has been a focal point for medical practitioners.

One specific lncRNA, MFSD4A-AS1, was found to be up-regulated in PTC tissues with lymph node metastasis. The up-regulated MFSD4A-AS1 acts as a ceRNA to promote lymphatic turnover by up-regulating VEGFA and VEGFC through the sponging effect on miR-30c-2-3p, miR-145-3p, and miR-139-5p. It also increases the expression of TGFBR2 and DUB USP15, partially activating the TGF-β signaling pathway. This ultimately facilitates the lymphangiogenic and invasive capacity of PTC cells for lymphatic turnover induction [116]. Another protein, DUB USP47, is upregulated in PTC tissues and protects the special AT-rich sequence binding protein 1 (SATB1) through deubiquitination. This induces PTC cell proliferation and invasion [117]. On the other hand, the E3 ligase SH3 domain containing ring finger 3 (SH3RF3) is upregulated due to reduced expression of miR-192-5p in PTC, which enhances the migration and invasion of cancer cells [118].

Additionally, some studies have found that the down-regulation of VHL is associated with the invasion and metastasis of PTC. This may be due to a decrease in the degradation of HIF-α, which is regulated by VHL [119]. However, another study found no correlation between *p*-VHL and VEGF proteins, suggesting that the role of *p*-VHL in PTC progression is independent of HIF-α [120].

3.7. MAPK signaling pathway

At least one driver somatic mutation is present in almost all (>96 %) PTC cases, with BRAF V600E being the most common mutation, which mimics the phosphorylation of BRAF and leads to activation of the MAPK signaling pathway [121]. It has been found that XIAP is increased in PTC with BRAF V600E mutation and correlates with inhibition of apoptosis and increased metastasis of the tumor [110,122]. However, it has also been suggested that although BRAF V600E mutation and XIAP are common in PTC, their presence does not appear to be correlated [123]. In addition to XIAP, VHL and Praja2 level was increased in BRAF V600E-mutated PTC, while in BRAF V600E-mutated metastases, the expression of VHL and TRIM16 was reduced compared to unmutated lymph node metastases [124,125]. In another study, Renaud et al. identified a novel BRAF fusion (BAIAP2L1-BRAF), the expression of which led to activation of the MEK1/2-ERK1/2 cascade and increased expression of the E3 ligase TRIM25, and enhanced cell proliferation [126]. There are

also a number of E3 ligases that directly regulate the MAPK signaling pathway. (carboxyl terminus of Hsc70-interacting protein) CHIP was found to be up-regulated in thyroid cancer, which promotes proliferation and tumorigenesis by activating the MAPK pathway and down-regulating FOXO3a [127]. RNF115 is also upregulated in PTC, which ubiquitinates degradation of cyclin-dependent kinase 10 (CDK10), which then activates the Raf-1 pathway in PTC cells and promotes PTC cell proliferation and invasion [128].RNF150, on the other hand, was found to be under-expressed in thyroid cancer, which ubiquitylates degradation of apoptosis signal regulating kinase 1 (ASK1), inhibits p38 phosphorylation, and ultimately down-regulates proliferation and migration of thyroid cancer cells [129].

3.8. Other pathways

Ubiquitination plays a crucial role in the occurrence and development of DTC in various ways. One important aspect is its impact on intracellular ROS levels. When ROS levels decrease below the normal threshold, proteins involved in thyroid cell function are affected. Martinez et al. discovered that the disruption of the kelch-like ECH-associated protein 1 (KEAP1)/Cullin 3 (CUL3)/ring-box 1 (RBX1) E3 ligase complex, often caused by promoter hypermethylation, leads to abnormal activation of NFE2-related factor 2 (NRF2), a substrate of the complex. This abnormal activation inhibits ROS production and contributes to the development of PTC [130]. Ferroptosis is an iron- and reactive oxygen species (ROS)-dependent form of cell death accompanied by massive lipid peroxidation-induced mitochondrial damage. In a recent study, DUB USP10 expression was increased in PTC, which promotes the expression of the ferroptosis inhibitor Glutathione Peroxidase 4 (GPX4) by elevating sirtuin 6 (SIRT6), thereby enhancing PTC proliferation, migration, and invasion [131].

Ubiquitination also plays a significant role in thyroid differentiation. Praja ring finger ubiquitin ligase 2 (PRAJA2) is found to be overexpressed in PTC but rarely expressed in ATC. Further studies have shown that Praja2 forms a stable complex with PKA and participates in the degradation of the R-subunit. By enhancing cAMP signaling, Praja2 confers metabolic and proliferative advantages to differentiated malignant tumors in DTC when TSH binds to its receptor and elevates cyclic adenosine monophosphate (cAMP) levels. However, ATC lacks TSH receptor expression and, therefore, cannot activate this pathway, leading to a gradual decrease in PRAJA2 levels [124].

Cellular autophagy is also a prominent topic in cancer therapy. In PTC, RNA binding motif protein 47 (RBM47) stabilizes SNHG5, which serves as a scaffold to recruit DUB USP21, inhibiting the ubiquitination of forkhead box O3 (FOXO3) and promoting its nuclear translocation. This ultimately activates autophagy and inhibits PTC cell proliferation [132]. Several other ubiquitin ligases or DUBs have been found to have altered expression in DTC. For example, E3 ligases glucose regulated protein 78 kD (Gp78), ubiquitination factor E4A (UBE4A), and ubiquitin like with phd and ring finger domains 1 (*UHRF1*) are overexpressed in DTC, while DUBs USP9X, UBP7, USP22, and the ovarian tumor protease domain-containing ubiquitin aldehyde-binding proteins 1 (*OTUB1*) are also overexpressed [133–137]. On the other hand, DUB USP18 is downregulated in DTC [138].

4. Medullary cancer

Research on ubiquitination modification and altered ubiquitinase expression in medullary thyroid cancer is limited but significant. Dilla et al. investigated MTT cell lines and observed that MDM2 was absent in these cells. However, overexpression of *MDM2* resulted in the down-regulation of Bcl-2, activation of caspase-2, and subsequent apoptosis of MTTs. The induced apoptosis by MDM2 was partially reversed by the overexpression of wild-type p53 and p19ARF [139]. These findings suggest a unique role of MDM2 in medullary thyroid cancer compared to other forms of thyroid cancer. Another study revealed that MDM2 sensitized human medullary thyroid cancer cells to ionizing radiation by increasing the levels and activity of the E2F Transcription Factor 1 (E2F-1) protein [140]. The role of MDM2 in differentiated thyroid cancer is distinct, possibly influenced by the absence of p53 in MTT cells. In this scenario, MDM2 could potentially facilitate apoptosis by interacting with other proteins like E2F-1. These studies emphasize the distinctive function of MDM2 in medullary thyroid cancer.

The role of VHL in medullary thyroid cancer warrants further investigation. A study identified mutations in the VHL gene in MTC tissues, resulting in increased expression of carbonic anhydrase IX (CAIX) and HIF1α in primary tumors and lymph node metastases [141]. However, another experiment indicates that somatic VHL gene alterations may not significantly contribute to the tumorigenesis of multiple endocrine neoplasia type 2-associated MTC [142]. Besides MDM2 and VHL, DUBs like Jab1 and Protein gene product 9.5 (PGP9.5) exhibit heightened expression in medullary thyroid cancer, playing a more substantial role in cell cycle regulation of MTC compared to DTC [143,144].

These studies emphasize the specific molecular mechanisms that differentiate medullary thyroid cancer from other types of thyroid cancer. Additional research is required to comprehensively investigate the impact of ubiquitination modification and altered ubiquitinase expression in medullary thyroid cancer.

5. Anaplastic thyroid cancer

ATC is the most aggressive form of thyroid cancer, and effective treatments for it remain a challenge. Recent research has shown that dysregulation of ubiquitination modification may be a potential way to treat ATC.

Yes-associated protein (YAP), a major factor in the Hippo tumor suppressor pathway, plays a critical role in ATC tumor progression. YAP is associated with cell proliferation, tumor metastasis, and chemotherapy resistance, making it an important target for cancer therapy. In one study, the E3 ligase TRIM11 was found to be high level in ATC due to transcriptional regulation of SRY-box transcription factor 13 (SOX13). High level of TRIM11 increased the mono-ubiquitination of YAP and inhibited the poly-ubiquitination of

K11- and k48-linked YAP, leading to increased stability of YAP and promoting ATC proliferation, migration, and drug resistance [145]. Another study found that the DUB ubiquitin C-terminal hydrolase L3 (UCHL3) was up-regulated in ATC cell lines, which decreased SHARPIN-induced YAP ubiquitination and stabilized YAP. This upregulation of YAP led to increased expression of SOX2, Nanog, KLF4, and Oct4, promoting ATC proliferation, migration, cancer sphere formation, and drug resistance. UCHL3 is also a direct transcriptional target of YAP/TEA domain transcription factor 4 (TEAD4), and upregulation of YAP increases the expression of UCHL3 [146].

The altered expression of IAP family members also plays a role in ATC progression. XIAP, a member of the IAP family, was found to be positively expressed in ATC tissues [107]. Additionally, decreased expression of miR-618 in ATC cells led to overexpression of *XIAP* and enhanced proliferation, migration, and invasion of ATC cells [147]. Livin, another member of the IAP family, expression product of *BIRC7*, was found to be highly expressed in ATC tissues. Knockdown of *BIRC7* reduced ATC cell viability and improved the effectiveness of radiotherapy [148].

Invasion and metastasis are responsible for the high malignancy of ATC, and abnormal ubiquitination modification plays a role in this process. High level of DUB USP22 was observed in ATC tissues and correlated with poor prognosis. Knockdown of DUB *USP22* inhibited Akt phosphorylation, reduced proliferation, migration, and invasion of ATC cells, and promoted apoptosis [149]. Hematological and neurological expressed 1 (HN1), expression products of *JPT1*, highly expressed in aggressive thyroid cancer, interacted with STMN1 to negatively regulate α-tubulin acetylation and promote cancer cell migration and invasion. Knockdown of *JPT1* upregulated ubiquilin 1 (UBQLN1) level, promoting UBQLN1 binding to stathmin 1 (STMN1) and increasing ubiquitin-mediated STMN1 degradation [150]. Ataxin 3 (ATXN3), significantly overexpressed in ATC tissues, enhanced eukaryotic translation initiation factor 5A2 (EIF5A2) stability through deubiquitylation, promoting ATC cell proliferation and metastasis [151]. *RBX1* overexpression was found to correlate with ATC migration and invasion ability. As an E3 ligase, RBX1 ubiquitinates scaffold/matrix attachment region binding protein 1 (SMAR1), down-regulating its expression. The SMAR1/histone deacetylase 6 (HDAC6) complex, involved in pyruvate kinase M1/2 (PKM) alternative splicing, is down-regulated as a result, down-regulating PKM1 and up-regulating PKM2, ultimately promoting ATC development by enhancing the Warburg effect [152].

In summary, dysregulation of ubiquitination modification and altered expression of IAP family members play significant roles in the progression of ATC. Targeting these pathways may provide potential therapeutic strategies for ATC treatment.

6. Ubiquitin-like protein

In addition to Ub, the Ub superfamily also includes ubiquitin-like proteins (Ubls), which are now categorized into two groups: ubiquitin-like proteins (type I) and ubiquitin-like domain proteins (type II). Recent studies on thyroid cancer have shown that Ubls (type I) are predominant. Like Ub, Ubls (type I) are transferred to lysine residues of target proteins by three enzymes - E1, E2, and E3. Ubls (type I) feature a distinct sequence motif with one or two glycine residues at the C-terminus for covalent linkage [153]. Despite structural similarities to Ub, Ubls serve different biochemical functions, playing roles in DNA repair, nuclear translocation, protein hydrolysis, translation, autophagy, and various cellular activities. This article focuses on the Ubls associated with thyroid cancer.

6.1. Sumoylation

Sumoylation is the process by which a small ubiquitin-related modifier (SUMO) attaches to a substrate by forming an isopeptide bond between its terminal glycine and the lysine of the substrate. SUMO, which shares 18 % sequence homology with ubiquitin and has a ubiquitin-like β-grasp fold core, has been identified in six human isoforms. These isoforms play a role in regulating the localization, stability, and activity of target proteins [154]. Evidence suggests that sumoylation may be implicated in tumorigenesis and the development of various cancers, with a particular focus on its role in thyroid cancer.

Platelet-derived growth factor-C (PDGF-C) belongs to the PDGF/VEGF family and has been implicated as a potential transcription factor in tumorigenesis, growth, metastasis, and drug resistance across various types of tumors. Research indicates that sumoylated PDGF-C exhibits enhanced stability and nuclear translocation to interact with chromatin. Interestingly, thyroid cancer cells demonstrate reduced levels of sumoylated PDGF-C, suggesting a potential regulatory role of sumoylation in gene expression [155]. This reduction in sumoylated PDGF-C levels may contribute to the progression of thyroid tumors towards a malignant state.

Coiled-coil domain containing 6 (CCDC6) is a tumor suppressor that interacts with the transcription factor cAMP responsive element binding protein 1 (CREB-1) to repress downstream oncogene transcription [156]. A study by Luise et al. found that the tumor suppressor effect of CCDC6 is influenced by sumoylation. CCDC6 is sumoylated at lysine sites 74, 266, and 424. When all three sites are sumoylated simultaneously, CCDC6 is unable to enter the nucleus, reducing its inhibitory effect on CREB-1 transcription factor. This weakened inhibition could potentially contribute to thyroid tumorigenesis [157].

The concept of cancer stem cells (CSCs) originates from oncogenic mutations in normal tissue stem cells, playing a crucial role in cancer recurrence, metastasis, and resistance to chemotherapy [158]. Therefore, successful cancer treatment necessitates the targeted eradication of CSCs to prevent disease relapse and spread. CD44 serves as a pivotal marker for identifying CSCs. In a study by Andrade et al., it was found that inhibiting the expression of transcription factor AP-2 α (TFAP2A) in ATC did not affect CD44 level; however, inhibiting TFAP2A through SUMO conjugation resulted in decreased *CD44* expression. Animal experiments further confirmed that utilizing a SUMO inhibitor effectively reduced the number of CD44-positive cells and decreased tumor size in mice with hormonal imbalances [159].

6.2. ISGylation

Interferon-stimulated gene 15 (ISG15), is a ubiquitin-like protein that plays a crucial role in the innate immune response against viral infections. It can either attach to target proteins (ISGylation) or function as a free or unattached protein. Recent studies have indicated that ISG15 is also involved in tumor development and progression, showing increased expression levels in various types of tumors, such as prostate and breast cancers [160].

Papillary thyroid microcarcinoma (PTMC) is a subtype of PTC characterized by tumors measuring 1 cm or less. Due to the challenges in identifying aggressive PTMC, treatment approaches for PTMC vary. In a study conducted by Lin et al., it was found that ISG15 promotes the proliferation and migration of cancer cells. Moreover, elevated levels of ISG15 protein were observed in lymph node metastatic PTMC, suggesting that ISG15 could serve as a biomarker for aggressive PTMC and aid in determining appropriate therapeutic strategies [161].

Karyopherin subunit alpha 2 (KPNA2) belongs to the nuclear transporter protein family, playing a role in facilitating the nuclear entry of the cancer stem cell-related transcription factor c-MYC. A recent study revealed that ISG15-mediated ISGylation of KPNA2 hinders its ubiquitination-induced degradation, thereby enhancing the nuclear translocation of c-MYC and preserving the cancer stem cell characteristics of ATC. This finding suggests a delicate interplay between ISGylation and ubiquitination, highlighting the potential therapeutic implications in tumor treatment by utilizing ISGylation inhibitors to promote the degradation of specific oncoproteins or alter their cellular localization [162].

7. Bioinformatics source

This review examines current bioinformatics research on protein ubiquitination modification globally. It summarizes previous studies focusing on the gathering of Ub/Ubls-related protein data, the development and evaluation of ubiquitination modification networks, and the forecasting of ubiquitination modification sites.

7.1. iUUCD 2.0

The iUUCD 2.0 (http://iuucd.biocuckoo.org/) serves as an updated systematic resource focused on ubiquitin and ubiquitin-like conjugations [163]. It encompasses 1230 E1s, 5636 E2s, 93343 E3s, 9548 DUBs, 30173 UBDs (ubiquitin-binding domain containing proteins), and 11099 ULDs (ubiquitin like domains) across 148 eukaryotic species, providing classification for E2, E3, DUB, UBD, and ULD. This resource consolidates detailed annotations for these proteins sourced from 68 public databases, covering 11 key areas such as cancer mutations, single nucleotide polymorphisms (SNPs), mRNA expression, DNA & RNA elements, protein-protein interactions, protein 3D structures, disease-associated variations, drug-target relations, post-translational modifications (PTMs), DNA methylation, and protein expression/proteomics. iUUCD 2.0 is freely accessible to all users, continually updated, and enhanced, making it a valuable tool for in-depth study and research on UB/UBL conjugations.

7.2. GPS-Uber

GPS-Uber is a hybrid-learning framework developed for the prediction of general and E3-specific lysine ubiquitination sites [164]. The developers utilized experimentally identified ubiquitination sites from the protein lysine modification database (PLMD) (http://plmd.biocuckoo.org/) and removed homologous sites through CD-HIT clustering, resulting in an initial training dataset of 61,161 ubiquitination sites. Subsequently, 10 sequence- and structure-based features including GPS, PseAAC, CKSAAP, OBC, aindex, ACF, PSSM, ASA, SS, and BTA were encoded using two-dimensional convolutional neural network (CNN), deep neural network (DNN), and penalized logistic regression (PLR) algorithms for model training. Additionally, E3-specific ubiquitination sites were manually collected from PubMed and classified into different E3 groups based on information from the Ubiquitin and Ubiquitin-like Conjugation Database (iUUCD) (http://iuucd.biocuckoo.org/) clusters. Migration learning was then applied on different E3 clusters to develop E3-specific models from the generalized model. Although GPS-Uber demonstrates higher accuracy in predicting general and E3-specific lysine ubiquitination sites compared to other tools, the hybrid-learning framework is continuously being optimized and the benchmark dataset expanded to support academic research endeavors.

7.3. GPS-SUMO 2.0

The identification of sumoylation sites and SUMO-interaction motifs (SIMs) in proteins is crucial for enhancing our understanding of SUMOs. GPS-SUMO 2.0 (https://sumo.biocuckoo.cn/) was developed to predict both covalent sumoylation sites and non-covalent SIMs in proteins [165]. The dataset comprises 59,069 sumoylation sites in 10,762 proteins and 163 SIMs in 102 proteins. By utilizing 11 types of sequence features and three machine learning algorithms (PLR, DNN, and Transformer), users can input one or more protein sequences or identifiers to receive predictions of sumoylation sites and SIMs. Furthermore, the tool incorporates information on sumoylation sites and SIMs from various public resources. Overall, GPS-SUMO 2.0 serves as a valuable tool for advancing research in the field of sumoylation.

Table 1
Characteristics of E3 ligase associated with thyroid cancer.

E3 ligase	cancer subtype	Target	signaling pathway	Function	References
RING finger family E3 ligases					
β-TRCP	PTC, ATC	VEGFR2	β-TRCP/VEGFR2, VEGFA/AKT, ERK1,2	Inhibit AKT signaling pathway, inhibit invasion, migration, inhibit angiogenesis	[43]
CBL	PTC	β-catenin	Circ-ITCH/miR-22-3p/CBL/β-catenin	Inhibit Wnt/β-catenin signaling pathway, inhibit proliferation, invasion, promote apoptosis	[83]
CDC23 (APC/C)	PTC, ATC	cyclin B, securin	LINC00514/miR-204-3p/CDC23/cyclin B, securin	Promote proliferation, invasion, migration, inhibit apoptosis	[101,102]
CHIP	PTC,ATC		CHIP/MAPK/FOXO3a/cyclin D1,p27	Overexpressed in thyroid cancer, Activate MAPK signaling pathway, promote proliferation	[127]
cIAP	FTC			Inhibit apoptosis, affect chemosensitivity	[109]
CUL3	PTC	NRF2		Maintain normal ROS levels	[130]
CUL4B	PTC	SIN1	AURKA/CUL4B/SIN1 (mTORC2)	Inhibit mTOR2/AKT signaling pathway, inhibit proliferation, migration	[51]
Deltex3	PTC	XRCC5		Inhibit invasion, migration	[57]
DTL	ATC	p21	DTX3/XRCC5/AKT	Promote a highly proliferative cancer stem cell-like phenotype	[170]
FBXW7	PTC		LncRNA SNHG4/miR-25/FBXW7/p-i-κB α, p-p65	Inhibit NF-κB signaling pathway, inhibit proliferation, promote apoptosis	[95]
FBXL19	FTC	TTF1	FBXL19/TTF1	No effect on tumor phenotype was observed	[171]
Gp78	PTC			Induce cancer stem cell(CSC) growth characteristics and express CSC markers	[133]
Livin	ATC			Inhibit apoptosis, Suppress radiation and chemotherapy sensitivity	[148]
MARCH6	PTC	DHX9	MARCH6/DHX9/AKT/mTOR	Activate AKT/mTOR signaling pathway, promote proliferation, migration, inhibit apoptosis	[148]
MDM2	PTC, FTC, MTC, ATC	p53	1.RasGRP3/RAS/AKT/MDM2 2. CircTP53/miR-1233-3p/MDM2	1.Promote proliferation, invasion, inhibit apoptosis in DTC and ATC. 2.Promote MTC apoptosis and enhance cancer cell sensitivity to ionizing radiation	[59,62,65,68,69,139,140]
MDM4	PTC, ATC	p53		1.Downregulate with tumor progression in PTC and associate with PTC non-multifocality 2. Increase survival of mice with wild-type p53 when reduced in ATC	[63–65]
Praja2	PTC, ATC	PKA	cAMP/Praja2/PKA	1.Overexpressed in PTC, Activate cAMP signaling pathway, promote proliferation 2.Low expression in ATC, can be used to monitor the degree of tumor malignancy	[124]
Rbx1	PTC, ATC	SMAR1, NRF2	Rbx1/SMAR1/PKM1	promote invasion, migration, promote carcinogenic potential, inhibit autophagy	[130,152]
RNF150	PTC	ASK1	RNF150/ASK1/p38	Downregulated in PTC, inhibit MAPK signaling pathway, inhibit proliferation, migration	[129]
SH3RF3	PTC		miR-192-5p/SH3RF3	Promote invasion, migration	[118]
SKP2	PTC, FTC, ATC	p27, PHLPP1	1.SKP2/PHLPP1/AKT 2. SKP2/p27	Promote proliferation, inhibit apoptosis and autophagy	[55,97,114]
TRIM11	ATC	YAP	SOX13/TRIM11/YAP	Activate Hippo signaling pathway, promote proliferation, migration, affect chemosensitivity	[145]
TRIM14	PTC	SOCS1	TRIM14/SOCS1/STAT3	Activate STAT3 signaling pathway, promote proliferation, inhibit apoptosis	[113]
TRIM16	PTC			In metastases with the BRAF-V600E mutation, expression was reduced compared to lymph node metastases without the mutation	[125]
TRIM25	PTC			MEK1/2-ERK1/2 downstream product, promote proliferation	[126]
TRIM26	PTC		TRIM26/PI3K/Akt	Silencing PI3K/AKT signaling pathway, inhibit proliferation, invasion, migration	[45]
TRIM28 (KAP-1)	PTC, FTC	DDX5	KAP-1/DDX5/β-catenin	Activate Wnt/β-catenin signaling pathway, promote proliferation, invasion, migration	[87,172]
TRIM29	PTC		TRIM29/P13K/AKT	Activate PI3K/AKT signaling pathway, promote proliferation, invasion, migration, inhibit apoptosis, affect chemosensitivity	[44]
TRIM30	PTC	Sox17	IL-22/TRIM30/Sox17/β-catenin	Regulate Wnt/β-catenin signaling pathway, promote proliferation, invasion, migration	[85]
TRIM44	PTC		TRIM44/β-catenin	Activate Wnt/β-catenin signaling pathway, promote proliferation, invasion, migration	[86]

(*continued on next page*)

Table 1 (*continued*)

E3 ligase	cancer subtype	Target	signaling pathway	Function	References
TRAF2	PTC			1.Selective activation of pro-inflammatory programs that may play a role in later stages of tumor progression.2.Inhibit TNFα-induced cell death	[89,93]
TRAF3	PTC			Not involved in NF-κB pathway activation, but increased expression in PTCs harboring the RET/PTC oncogene	[90]
TRAF6	PTC, FTC			Lowly expressed in DTC and may be involved in selective activation of pro-inflammatory programs	[89,91,173]
UHRF1	PTC			Upregulate ERα/ERβ expression ratio, promote proliferation, invasion and migration	[135]
VHL	PTC, FTC, MTC, ATC	HIF-α	1.miR-21/VHL/PI3K/AKT 2. VHL/Dvl	Inhibit PI3K/AKT signaling pathway, inhibit proliferation, invasion, and angiogenesis	[46,119,120, 141]
XIAP	PTC, FTC, MTC, ATC		OIP5-AS1/miR-429/XIAP	Promote proliferation, invasion, migration, inhibit apoptosis, affect chemosensitivity	[104,105,107, 108,110–112, 147,166]
ZNRF2	PTC		TTN-AS1/miR-153-p/ZNRF2	Promote proliferation, invasion, migration	[72]
ZNRF3	PTC	FZD and LRP 5/6 complexes	1.miR-146b-5p/ZNRF3/FZD, LRP complexes 2. ZNRF3/Wnt/β-catenin/TCF4	Inhibit Wnt/β-catenin signaling pathway, inhibit proliferation, invasion, migration	[73,74]
HECT family E3 ligases					
HECW1	Normal thyroid cell	TTF1	HECW1/TTF1/TG, NIS	inhibit proliferation, migration	[171]
HUWE1	PTC, FTC, ATC	N-MYC, C-MYC, MCL1, MDM2	HUWE1/N-MYC, C-MYC, MCL1, MDM2	Inhibit proliferation, invasion, migration, enhance chemosensitivity	[65,136]
ITCH	PTC, ATC			Promote proliferation	[174]
SMURF1	PTC	KISS-1	SMURF1/KISS-1/NF-κB	Activate NF-κB signaling pathway, promote proliferation, invasion, migration	[94]
WWP1	PTC	PTEN	WWP1/PTEN/PI3K/AKT	Activate PI3K/AKT signaling pathway, promote proliferation, invasion, migration, inhibit apoptosis	[47]

Table 2
Characteristics of DUBs associated with thyroid cancer.

DUB	cancer subtype	Target	signaling pathway	Function	References
1.The ubiquitin-specific proteases (USPs)					
CYLD	PTC		MiR-181b/CYLD/NF-κB	Inhibit proliferation	[76]
USP9X	PTC			Promote migration	[136]
USP7	PTC	TBX3	USP7/TBX3/p57KIP2	Promote proliferation and tumorigenesis	[100,136]
USP13	PTC			Promote proliferation	[175]
USP15	PTC	TGFβR	MFSD4A-AS1/USP15/TGF-β/SMAD	Promote invasion, migration, induces lymphangiogenesis	[116]
USP18	PTC			Promote proliferation	[138]
USP21	PTC	FOXO3	RBM47/SNHG5/USP21/FOXO3/ATG3, ATG5	Inhibit proliferation, promote autophagy	[132]
USP22	PTC, ATC	H2A,H2B		Strongly correlated with tumor size, extracapsular infiltration, multifocality, lymph node metastasis, distant metastasis and TNM staging	[149,176]
USP33	PTC	Robo1	USP33/Robo1	Promote invasion, migration, inhibit apoptosis	[115]
USP47	PTC	SATB1	USP47/SATB1	Promote proliferation, invasion, migration	[117]
2.The ovarian tumor proteases (OTUs)					
OTUB1	PTC	EYA1	OTUD1/EYA1	Promote proliferation	[137]
OTUD3	PTC	PTEN	MYC/BGL3/OTUD3/PTEN	Inhibit proliferation, migration	[50]
3.The ubiquitin C-terminal hydrolases (UCHs)					
PGP9.5	MTC	Cyclin		Promote proliferation	[143]
UCHL3	ATC	YAP	UCHL3/YAP/CTGF, CYR61, ANKRD1	Promote proliferation, migration, Suppress chemotherapy sensitivity	[146]
4.The Josephine family					
ATXN3	ATC	EIF5A2	ATXN3/EIF5A2	Promote proliferation, migration	[151]
5.Jab1/MPN domain associated metalloisopeptidases DUBs (JAMMs)					
Jab1	PTC, MTC	ANGPTL2, p27	1.CSN5/ANGPTL2 2. CSN5/p27	Promote proliferation, migration	[98,144]
CSN6	PTC		CSN6/β-Trap/β-catenin	Promote proliferation, migration	[80]

Table 3
Drugs targeting ubiquitinating enzymes or DUBs for thyroid cancer.

Drugs	Mechanism and Application	References
3-Deazaneplanocin A (DZNep)	DZNep contributes to the inhibition of cancer cell growth by causing p53 protein accumulation through the upregulation of USP10 expression	[177]
APG115	APG115 is an MDM2-p53 interaction antagonist that blocks the cell cycle and induces apoptosis in dedifferentiated papillary thyroid cancer	[70]
Bendamustine	Bendamustine inhibits RBR-type E3 HOIP for redifferentiation of RAI-refractory thyroid cancer	[178,179]
Curcumin	Curcumin down-regulates Skp2 and XIAP, inhibits proliferation, migration and invasion of DTC and ATC, and promotes the re-differentiation of poorly differentiated cancer. Curcumin also inhibits the proliferation of MTC, induces apoptosis, and reduces the secretion of calcitonin	[180–186]
Epigallocathesin-3-gallate (EGCG)	EGCG is an MDM2-p53 interaction antagonist that inhibits proliferation, migration, invasion, angiogenesis, and induces apoptosis in DTC and ATC	[187,188]
GDC-0152	GDC-0152 is an IAP inhibitor that induces TRAIL sensitivity and promotes apoptosis in FTC	[109]
Indole-3-carbinol(I3C)	I3C, a NEDD4-1 inhibitor, blocks the cell cycle in DTC and induces apoptosis	[189]
KRT-232	MDM2 inhibitor, blocks the cell cycle and induces apoptosis	[167]
Quercetin	Quercetin down-regulates Skp2, inhibits DTC proliferation, migration, and invasion, and up-regulates NIS expression in cancer cells. Quercetin also inhibits MTC proliferation	[190–193]
Silibinin	Silibinin downregulates Skp2, inhibits TPC migration, invasion, and ATC proliferation.	[194,195]
TCID	UCHL3 inhibitor TCID inhibits growth and metastasis of ATC cells	[146]
Triptolide	Triptolide inhibits cell proliferation and induces apoptosis in thyroid cancer by up-regulating p53 through inhibition of MDM2, and the effect is further enhanced when combined with hsp90 inhibitor BIIB021.	[196–198]

8. Conclusions and outlook

Thyroid cancer, a prevalent malignant tumor of the endocrine system, has been the subject of recent studies highlighting the significant role of ubiquitination modifications in its pathogenesis. Ubiquitinating enzymes and DUBs are key actors in this modification process and have been implicated in thyroid carcinogenesis. They are crucial targets for TC development (refer to Table 1 and Table 2). For instance, the elevated expression of *XIAP*, a ubiquitinating enzyme, has been associated with unfavorable prognoses in various thyroid cancer subtypes like DTC, MTC, and ATC [104,147,166]. Discrepancies in enzyme expression levels, such as MDM2 being upregulated in DTC but scarce in MTC, may elucidate the resistance of MTC to radiotherapy and chemotherapy [68,139]. Moreover, Praja2, another enzyme, exhibits significant overexpression in DTC but minimal expression in ATC, indicating variations in ubiquitinating enzyme expression during the de-differentiation process of thyroid cancer [124]. These discoveries aid in comprehending the similarities and distinctions among different thyroid cancer subtypes, offering valuable insights for clinical diagnosis and treatment. However, existing studies on ubiquitinating enzymes and DUB in thyroid cancer have certain limitations. Most research has focused on DTC, which has shown more promising therapeutic outcomes, while there is a need for more breakthroughs in understanding MTC and ATC, which are more aggressive forms of thyroid cancer. Additionally, studies on ubiquitination in thyroid cancer have predominantly explored its effects on proliferation, invasion, apoptosis, and other functions, with limited research on its role in dedifferentiation, pyroptosis, ferroptosis, and cuproptosis. Furthermore, there is a lack of comprehensive studies on UBLs in the context of thyroid cancer, leaving significant gaps in our understanding. For instance, Jab1, a NEDD8-specific protease, is found to be upregulated in both DTC and MTC, yet there is a notable absence of neddylation studies in thyroid cancer research.

While current treatment options for thyroid cancer are well-established, they may not be sufficient for advanced cases. Therefore, the development of novel drugs to improve the prognosis of advanced thyroid cancer patients is imperative. Ubiquitinating enzymes and DUBs have emerged as promising therapeutic targets. For example, the upregulation of MDM2 has been shown to increase the sensitivity of MTC to radiation therapy [140]. Recent research has demonstrated that combining KRT-232, an MDM2 inhibitor, with the MEK inhibitor Selumetinib can enhance oncogenic effects in PTC [167]. Furthermore, various other drugs have exhibited efficacy in controlling thyroid cancer progression in both in vivo and in vitro experiments (Table 3). Moving forward, targeted drugs will continue to be explored for thyroid cancer treatment, with a focus on refining studies targeting ubiquitinating enzymes and DUBs. This may involve identifying and quantifying ubiquitination-modified proteins using immunoassay or mass spectrometry, as well as pinpointing abnormal protein ubiquitination-modification sites in tumors through bioinformatic design libraries. Subsequently, corresponding small-molecule drugs can be developed for targeted treatment.

Therapeutic strategies targeting ubiquitinating enzymes or DUBs have expanded to include translational therapies based on E3 ligase research. One such technology is proteolysis-targeting chimeras (PROTAC), which leverages the Ubiquitin-Proteasome System to degrade target proteins [168]. PROTAC comprises three components: an E3 ubiquitin ligase ligand, a target protein ligand, and a specially designed linker structure. When administered to a patient, the target protein ligand of PROTAC binds to the target protein, while the E3 ubiquitin ligase ligand binds to the substrate-binding region of the E3 ubiquitin ligase in the cell. This interaction 'brings' the target protein closer to the E3 ubiquitin ligase through the linker, facilitating the ubiquitination degradation of the target protein [169]. Unlike traditional small molecule drugs, PROTAC can theoretically bind to any part of the protein, require lower drug concentrations for therapeutic effects, and are less prone to drug resistance, making them a potential tool for treating refractory thyroid cancer. However, the limited number of E3 ubiquitin ligase targets compatible with PROTAC remains a bottleneck in its widespread development. In conclusion, whether through small molecule drugs or PROTAC, the study of ubiquitination holds promise for combating thyroid cancer and offering valuable insights for its diagnosis and treatment.

Data availability statement

This study is a review and the raw data are available in references studies.

CRediT authorship contribution statement

Xingmin Xiong: Writing – original draft. **BenBen Huang:** Writing – review & editing. **Zhe Gan:** Writing – review & editing. **Weixiang Liu:** Visualization. **Yang Xie:** Writing – review & editing. **Jianing Zhong:** Writing – original draft. **Xiangtai Zeng:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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