Ubiquitination and N^6-methyladenosine in cancer: Convergent regulation of oncogenic signaling pathways (Review)

HAILONG LI and XUELIN LU

Department of Pathology, Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City), Changde, Hunan 415000, P.R. China

Received December 22, 2025; Accepted April 24, 2026

DOI: 10.3892/ol.2026.15652

Abstract. Ubiquitination and N^6-methyladenosine (m^{6}A) RNA methylation constitute two fundamental layers of post-translational and post-transcriptional regulation that coordinately govern gene expression in cancer. These regulatory systems exhibit intricate crosstalk, revealing that they frequently converge on shared oncogenic signaling pathways to fine-tune malignant cell behaviors. Cooperative regulation by ubiquitination and m^{6}A is involved in modulating core cancer-driving circuits, including the PI3K-AKT and NF-κB pathways, thereby taking part in tumor cell proliferation, metastatic dissemination, immune evasion, metabolic adaptation and resistance to targeted therapies and chemotherapy. The interaction between them forms intricate feedback loops and exhibits context specificity, with the same regulatory axis capable of promoting or restraining tumorigenesis depending on cell types, mutation background and microenvironmental cues. Elucidating the molecular mechanisms underlying ubiquitin-m^{6}A crosstalk is thus key for developing next-generation precision oncology strategies. Notably, components of these pathways such as ubiquitin ligases, deubiquitinases and m^{6}A writers, erasers and readers, have been regarded as potential diagnostic biomarkers and therapeutic targets. Future advances relying on integrative multi-omics profiling, sophisticated functional models and rigorous *in vivo* validation are essential to unravel the complexity of these multi-layered regulatory networks. Such insights may ultimately enable the rational design of therapies that exploit ubiquitin-m^{6}A crosstalk to more effectively suppress cancer progression.

Correspondence to: Dr Xuelin Lu, Department of Pathology, Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City), 388 Renmin East Road, Changde, Hunan 415000, P.R. China
E-mail: luxuelin0819@163.com

Abbreviations: m^{6}A, N^6-methyladenosine; PTM, post-translational modification; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; DUB, deubiquitinating enzyme; TRIM, tripartite motif containing; PROTAC, proteolysis-targeting chimera; METTL, methyltransferase-like; YTHDF1 YTH, N6-methyladenosine RNA binding protein 1; FTO, fat mass and obesity-associated protein; CYLD, cylindromatosis lysine 63 deubiquitinase; BDNF, brain-derived neurotrophic factor; PLK1, polo-like kinase 1; ncRNA, non-coding RNAs; TRAF, TNF receptor-associated factors; PDK, 3'-phosphoinositide-dependent kinase; HCC, hepatocellular carcinoma; UBE, ubiquitin-conjugating enzyme; AML, acute myeloid leukemia; EMT, epithelial-mesenchymal transition; caRNA, chromatin-associated RNA

Key words: ubiquitination, N^6-methyladenosine, cancer, oncogenic signaling pathways, therapeutic innovation

Contents

1. Introduction

Among the diverse regulatory mechanisms in cell biology, post-translational modifications are vital in the process of tumorigenesis (1). Ubiquitination, a pivotal post-translational modification (PTM), involves the covalent attachment of the 76-amino-acid ubiquitin to substrate proteins and thus regulates their stability, activity and intracellular signaling (2). Such modification is catalyzed by a multi-step enzymatic cascade consisting of ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2) and ubiquitin ligases (E3) (3). Ubiquitination contributes to cell-cycle control and genome stability, as well as influencing cellular growth, proliferation and death. The dysregulation of ubiquitination in cancer frequently degrades tumor suppressors such as p53, thereby facilitating the proliferation and metastasis of tumor cells (4). Furthermore, counterbalancing ubiquitination, deubiquitinating enzymes (DUBs) remove ubiquitin moieties and disassemble ubiquitin chains, thereby playing a key role in maintaining ubiquitin system homeostasis and restraining

signal transduction, thus preventing pathway overactivation in cancer (5).

N^6-methyladenosine (m^{6}A) is among the most prevalent RNA modifications, gaining increasing attention in recent years (6). m^{6}A modulates the stability and translational efficiency of mRNA, and is also indispensable in RNA splicing and decay (7). Accumulating evidence indicates that m^{6}A regulates gene expressions implicated in tumorigenesis, thereby directly influencing malignant phenotypes (8). For instance, m^{6}A-modified circNEK11 has been reported to promote hepatocellular carcinoma (HCC) progression via the miR-1236-3p/glutathione peroxidase 2 axis (9). m^{6}A is also engaged in tumor micro-environment remodeling by altering intercellular signaling networks (10).

Recent studies have uncovered extensive crosstalk between ubiquitin-dependent and m^{6}A-dependent regulation, such that these pathways do not act in isolation but converge on shared molecular nodes and signaling circuits (11,12). Mechanisms of interplay include ubiquitin-mediated control of the abundance and activity of m^{6}A writers/erasers/readers, m^{6}A-dependent regulation of mRNAs encoding components of ubiquitin pathways, and coordinated actions at the chromatin-transcription interface where co-transcriptional m^{6}A deposition and histone ubiquitination collectively influence RNAPII dynamics and nascent RNA processing (13). Through these interactions, ubiquitination and m^{6}A cooperatively modulate core oncogenic signaling networks, for example, PI3K-AKT (14), Wnt/β-catenin (15) and NK-κB (16), thereby governing proliferation, metastasis, immune interactions and resistance to therapy. Hence, a systematic dissection of their reciprocal regulation and pathogenic mechanisms helps deepen the current understandings of tumor biology and may uncover new therapeutic avenues.

The present review synthesizes current knowledge on the molecular mechanisms by which ubiquitination and m^{6}A intersect to regulate oncogenic signaling. The core enzymology and functional consequences of each modification were first summarized, and mechanistic examples of crosstalk at the levels of protein, RNA and chromatin were subsequently summarized. The ways through which these interactions impinge on major cancer signaling pathways were also addressed. Ultimately, the present review considers translational implications and outlines challenges and future directions, emphasizing the need for integrated multi-omics and refined functional models to disentangle context specificity and to exploit the ubiquitin-m^{6}A axis for cancer therapy.

2. Ubiquitination in cancer

Ubiquitin is a 76-amino-acid protein widely expressed in eukaryotes (17). Ubiquitination, referring to the covalent attachment of ubiquitin to substrate proteins, is the second most common PTM after phosphorylation (2). This modification is facilitated by a highly specific ATP-dependent enzymatic cascade (18). This process involves a series of steps that utilize ubiquitin along with E1 enzymes for activation, E2 enzymes for conjugation, and E3 ligases for transfer. Ubiquitination serves as a dynamic post-translational protein modification conserved across eukaryotes (Fig. 1). The activation of ubiquitin starts with the formation of a thioester bond between the thiol group of E1 and the carboxyl group of the ubiquitin molecule, driven by ATP. Once activated, E1 transfers the ubiquitin to E2 through a transesterification reaction, binding it to a cysteine residue at the active site of E2. E2 then facilitates the transfer of ubiquitin to E3, which in turn catalyzes the ubiquitin to the substrate and releases E2, thereby generating a defined ubiquitinated product (19).

Recent studies have suggested that ubiquitination, together with its reversal by DUBs, plays instrumental roles in regulating multiple hallmarks of cancer, including evasion of growth-suppressive signals, reprogramming of energy metabolism and modulation of tumor immune responses (20-22). For instance, E3 ubiquitin ligase Tripartite Motif Containing (TRIM)-21-mediated ubiquitination of Sohlh2 inhibits M2 macrophage polarization, thus suppressing the progression of triple-negative breast cancer and colorectal cancer (23,24). Additionally, research by Chen *et al* (25) shown that LHPP disrupts energy metabolism in glioblastoma by promoting the ubiquitin-dependent degradation of PKM2. Moreover, USP13 stabilizes NLRP3 and enhances inflammasome activation by preventing TRIM31-mediated ubiquitination and degradation of NLRP3 (26). A recent study found that UCHL3 deficiency promoted ENO1 ubiquitination, attenuated the AKT/CCND1 signaling axis, suppressed the progression of gastric cancer and enhanced the sensitivity to palbociclib (27).

Previous reports highlighted emerging approaches involving ubiquitination in cancer therapy, such as proteolysis-targeting chimeras (PROTACs) and molecular glues (28,29). The PROTAC technology serves as an effective platform for targeted protein degradation and is advancing the development of related drugs (30). ARV-110 (bavdegalutamide) and ARV-471 (vepdegestrant) represent the forefront of PROTAC drug development currently in clinical practice, and both have progressed to Phase II trials (31,32). Meanwhile, ARV-110 is designed to selectively target the androgen receptor and promote its degradation through the recruitment of E3 ligases (33,34). Previous data from the first-in-human Phase I study indicated that ARV-110 demonstrated satisfying safety and tolerability in patients with metastatic castration-resistant prostate cancer (35). Compared with PROTACs, molecular glues are smaller molecules, which simplifies their chemical optimization. To date, several molecular glue degraders have been identified (36). Notably, CC-90009 has been shown to facilitate the ubiquitin-mediated degradation of G1 to S phase transition protein 1 by recruiting the E3 complex CUL4-DB1-CRBN-RBX1 and it is also undergoing Phase II clinical trials for treating leukemia (37).

3. m^{6}A modification in cancer

The m^{6}A denotes methylation at the N6 position of adenosine within RNA and constitutes the most abundant internal modification of eukaryotic mRNA (38). It is broadly distributed across transcripts but preferentially occurs at the consensus RRACH motif (R=A/G; H=A/C/U), and is often enriched near the stop codons (39). Genome-wide analyses further indicate that m^{6}A deposition is generally quicker and more efficient within coding sequences than in the 3' untranslated regions (40). Functionally, m^{6}A impacts nearly every step of mRNA metabolism: It regulates nuclear processing and export,

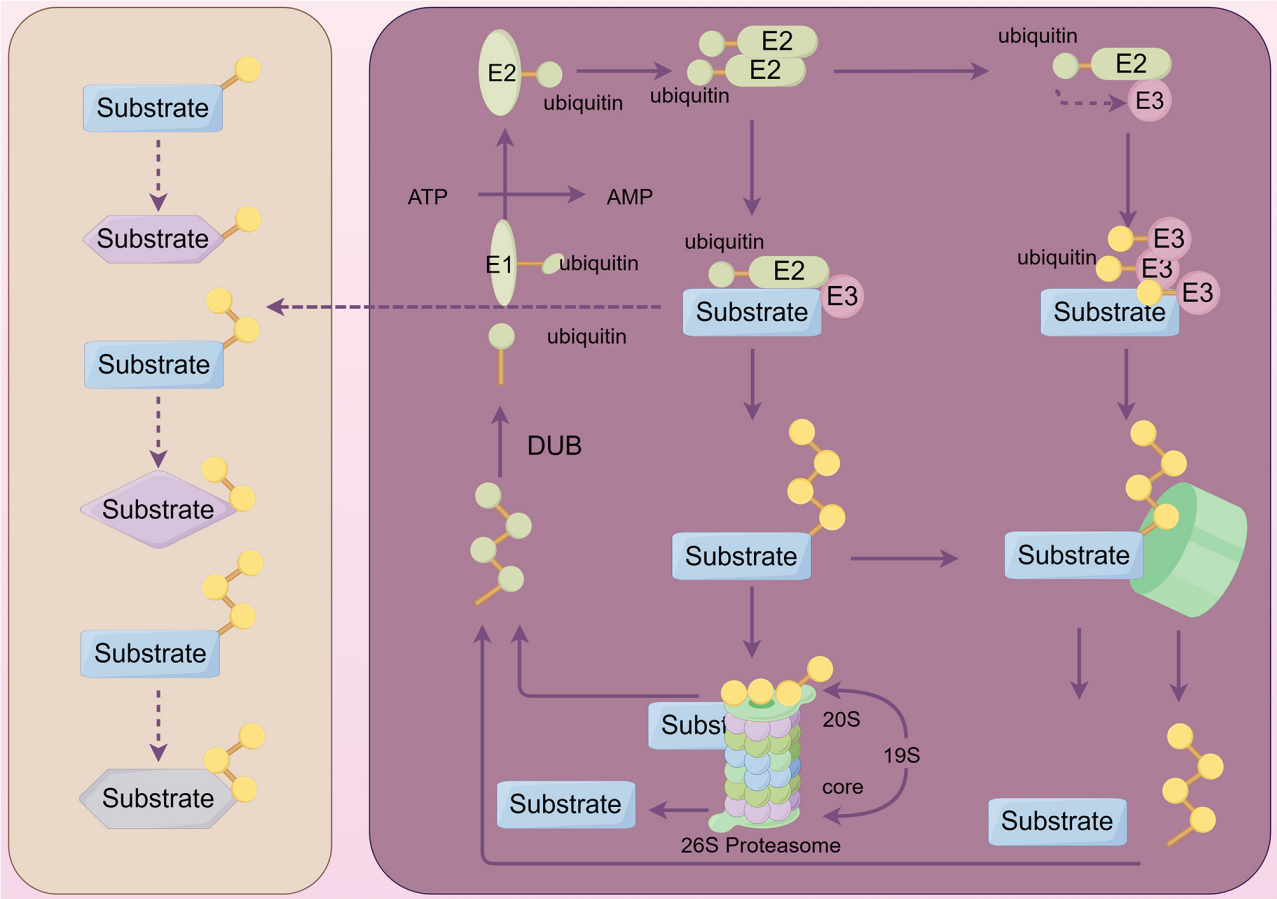

Figure 1. Schematic representation of the ubiquitin-proteasome-mediated protein degradation pathway. The process is initiated by the ATP-dependent activation of ubiquitin via an E1 activating enzyme, which catalyzes the formation of a thioester bond between its catalytic cysteine and the C-terminal glycine of ubiquitin. The activated ubiquitin is subsequently transferred to the E2 conjugating enzyme through a transesterification reaction. The E3 ubiquitin ligase then mediates the final conjugation step, facilitating the transfer of ubiquitin from the E2 to a lysine residue on the substrate protein via an isopeptide bond. The resulting ubiquitinated substrate is ultimately targeted to the 26S proteasome for proteolytic degradation. Figure generated using Adobe Illustrator (v29.8.1.2, Adobe Systems, Inc.). E1, Ubiquitin - activating enzyme; E2, Ubiquitin - conjugating enzyme; E3, Ubiquitin ligase; ATP, adenosine triphosphate; AMP, adenosine monophosphate; DUB, deubiquitinating enzyme.

modulates cytosolic translation efficiency and transcript turnover, and thereby enables precise spatiotemporal control of gene expression. Structurally, m^{6}A alters local base stacking via enhancing π-π interactions in unpaired regions, which reduces conformational flexibility and stabilizes tertiary RNA structures (41). Mechanistically, m^{6}A promotes translation by recruiting or modulating eukaryotic initiation factors, thereby enhancing the translation of capped mRNAs (42). It is known that m^{6}A is implicated in physiological processes, including immune and inflammatory responses (43). The m^{6}A mark is dynamic and reversible: It is installed by methyltransferase 'writers', removed by demethylase 'erasers' and interpreted by specific 'reader' proteins that mediate downstream effects on RNA fate (44). This epitranscriptomic circuitry permits combinatorial, context-dependent regulation of RNA metabolism, enabling m^{6}A to act as a tunable molecular rheostat that integrates extracellular cues with intracellular regulatory networks. Unlike genetic mutations, m^{6}A modifications present few alterations to the nucleotide sequence. Instead, a rapid and reversible mechanism to reprogram transcriptome function is provided, and gene expression outputs are dynamically adjusted in response to changing cellular or environmental cues (45).

Dysregulation of the m^{6}A methylation apparatus, which is indispensable for normal cellular homeostasis, is capable of promoting carcinogenesis and fostering resistance to therapy, highlighting its pivotal role in cancer (46) (Fig. 2). The impact of this progress is highly context-specific: Methyltransferase-like 3 (METTL3)-driven hypermethylation is associated with increased proliferation, metastasis and apoptosis resistance in breast cancer and implicated in several lung cancer subtypes, whereas METTL14 over-expression has been reported to limit metastatic spread in HCC (47). Given the involvement of m^{6}A in a broad spectrum of tumor-relevant processes, including cell-cycle progression, epithelial-mesenchymal transition (EMT), angiogenesis, dissemination, immune modulation and treatment response, its functions must be defined in a cancer-type-specific manner to inform precision interventions (48). In clinical practice, m^{6}A landscapes and the expression of m^{6}A regulators hold promise as prognostic biomarkers. For example, higher levels of YTH m^{6}A RNA binding protein 1 (YTHDF1) and insulin-like growth factor 2 mRNA-binding protein 2 (both are m^{6}A readers) associate with worse overall survival in HCC (49). However, therapeutic targeting of the m^{6}A machinery faces substantial hurdles, including the omnipresence of RNA

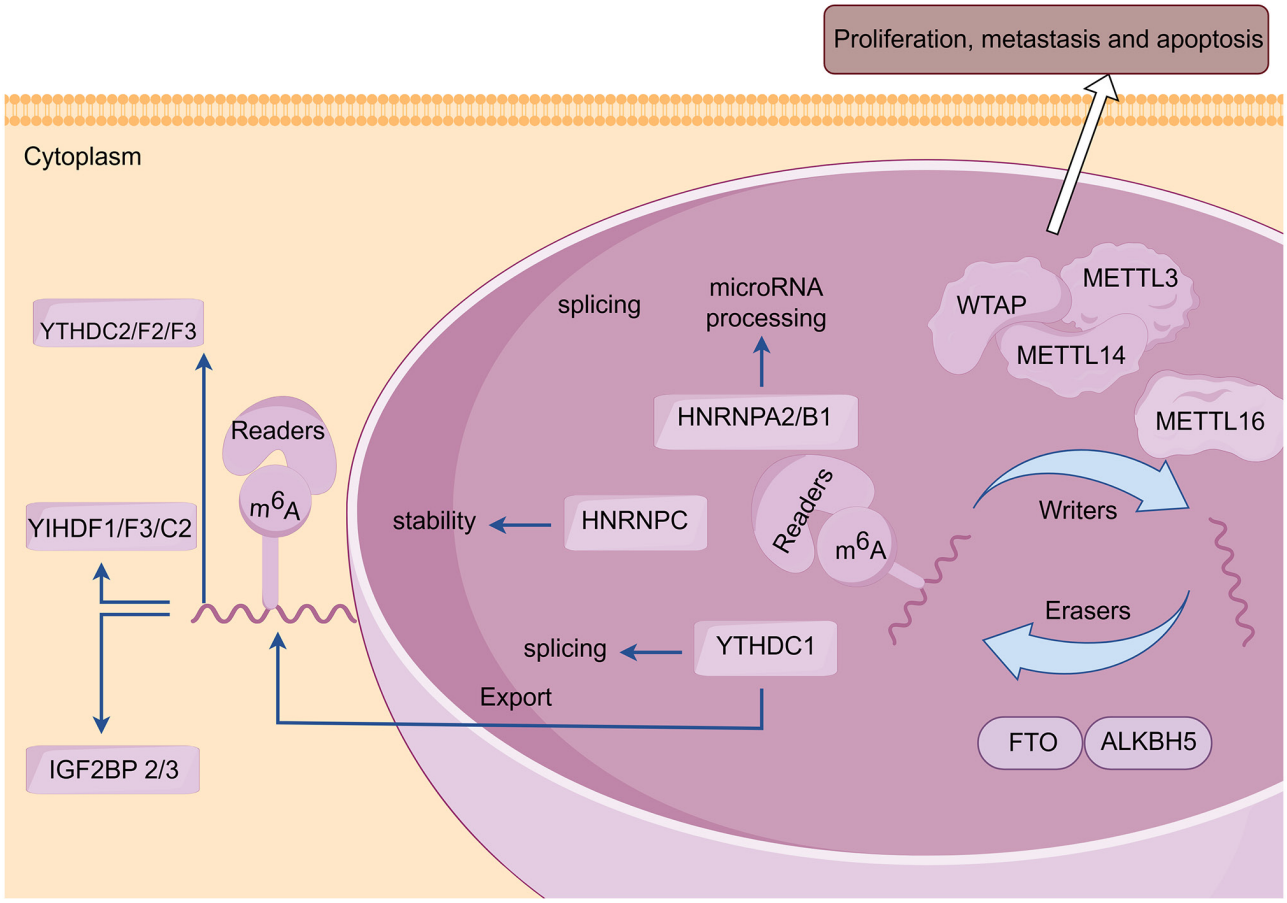

Figure 2. Schematic representation of the m6A modification in cancer. This figure illustrates the reversible m6A enzymatic cycle and its role in governing the fate of mRNA transcripts within oncogenic signaling pathways. The modification is installed by 'writer' complexes, such as METTL3 and METTL14, which catalyze methylation at the RRACH consensus motif, and is removed by 'eraser' demethylases such as FTO and ALKBH5. These marks are subsequently interpreted by specific 'reader' proteins, including members of the YTH family and IGF2BPs, that mediate downstream effects on RNA metabolism, such as splicing, nuclear export, transcript stability and translational efficiency. Dysregulation of these regulators disrupts normal cellular homeostasis and promotes hallmarks of cancer, such as cell-cycle progression, epithelial-mesenchymal transition, metastatic dissemination and therapeutic resistance, in a highly context-specific manner. Figure generated using Adobe Illustrator (v29.8.1.2, Adobe Systems, Inc.). METTL3, methyltransferase-like 3; HNRNPA2/B1, heterogeneous nuclear ribonucleoprotein A2/B1; YTHDC1, YTH domain-containing 1; m6A, N6-methyladenosine; FTO, fat mass and obesity-associated protein; ALKBH5, ALKB homolog 5; WTAP, Wilms' tumor 1-associated protein; YTHDC2/F2/F3, YTH domain - containing 2/F2/F3; IGF2BP 2/3, insulin-like growth factor 2 mRNA-binding protein 2/3; METTL14, methyltransferase-like 14.

modifications, their pleiotropic and occasionally opposing functions, risks of off-target and toxic effects, as well as delivery constraints (50). Despite these challenges, targeted strategies such as small-molecule inhibitors and antisense oligonucleotides, are under active pre-clinical and early-phase clinical investigation.

4. m^{6}A modification and key cancer-related pathways

Recent research highlights the intricate regulatory roles of m^{6}A modification in cellular signaling pathways, positioning this epitranscriptomic mark as a key target for unraveling pathogenic molecular mechanisms and advancing targeted therapeutic strategies (51). Of note, the major signaling pathway modulated by m^{6}A modification include pathways such as NF-κB, PI3K-AKT, MAPK, Wnt and mechanistic target of mTOR (52). These signaling pathways are essential in cellular growth regulation, proliferative signaling, lineage commitment and programmed cell death (53), the dysregulation of which is mediated by m^{6}A modification and is associated to the development of various diseases, especially in the context of oncogenic transformation.

The NF-κB pathway. Specifically, Steroid receptor coactivator-1 facilitates METTL3-mediated m^{6}A modification by coactivating NF-κB and promotes the malignant progression of glioblastoma (54). STAT1 activation and m^{6}A-mediated enhancement of IL15RA expression cooperatively promote metastatic progression in clear cell renal cell carcinoma by activating the ZEB1/NF-κB signaling axis (55). METTL3 promotes bladder cancer progression via the AF4/FMR2 family member 4/NF-κB signaling network (56). Fat mass and obesity-associated protein (FTO) enhances oral squamous cell carcinoma progression via m^{6}A-dependent stabilization of PKM2 mRNA through YTHDF2 modulation (57). Two key regulators of the NF-κB pathway, namely IKBKB and RELA, have been identified as direct targets of METTL3-catalyzed m^{6}A methylation (58). The cylindromatosis lysine 63 deubiquitinase (CYLD)/NF-κB pathway has been confirmed to be downstream of YTHDC2, and this axis is mediated by

m^{6}A modification in lung cancer (59). YTHDC2 exerts its anti-tumor effects via the CYLD/NF-κB signaling pathway, a process modulated by m^{6}A modification.

The PI3K-AKT pathway. The PI3K-AKT pathway is a central intracellular signaling cascade involved in tumor growth, therapeutic resistance and metastasis, and is frequently dysregulated in human cancer (60). FTO promotes GnRH expression by demethylating m^{6}A sites on brain-derived neurotrophic factor (BDNF) and activating the BDNF/PI3K-AKT axis (61). It is also known that METTL14 suppresses colorectal cancer progression by modulating the PI3K-AKT pathway and inhibiting SOX4-driven EMT (62). YTHDF1 enhances the translation of polo-like kinase 1 (PLK1) through m^{6}A-modified PLK1 mRNA, leading to hyperactivation of PI3K-AKT signaling. This YTHDF1-PLK1-PI3K-AKT axis is key for prostate cancer progression and represents a potential therapeutic target (63). In addition, studies have shown that WTAP/YTHDF1-mediated m^{6}A modification upregulates PXDN, which remodels the extracellular matrix and activates the PI3K-AKT pathway, thereby promoting nasopharyngeal carcinoma progression (64,65). Wang *et al* (66) found that METTL3-mediated m^{6}A methylation of the long non-coding RNAs (ncRNA) DUXAP8 promoted esophageal squamous cell carcinoma progression by activating the PI3K-AKT signaling pathway. Moreover, according to previous research findings, m^{6}A-modified circDCP2 accelerates carbon black nanoparticle-induced malignant transformation of human bronchial epithelial cells by activating the PI3K-AKT pathway and disrupting macrophage homeostasis (67,68) (Fig. S1).

5. Ubiquitination in oncogenic signaling pathways

Ubiquitination, a reversible PTM orchestrated by the sequential action of E1, E2 and E3, and antagonized by DUBs, serves as a pivotal molecular switch in regulating the spatiotemporal dynamics of oncogenic signaling pathways (69). Through dictating the stability, sub-cellular localization and protein-protein interactions of key signaling molecules, the balance between E3 ligase-mediated ubiquitination and DUB-mediated deubiquitination fine-tunes the amplitude and duration of signaling outputs, thereby governing key cellular processes such as proliferation, survival, migration and metabolism, all of which are dysregulated in cancer (70). In this section, how E3 ligases and DUBs modulate the NF-κB, and PI3K-AKT pathway is summarized, highlighting the symmetrical regulatory networks that underpin tumorigenesis and progression.

Modulation of NF-κB signaling pathway by E3 ligases and DUBs. The NF-κB family of transcription factors (including RelA/p65, RelB, c-Rel, p50 and p52) is necessary in mediating inflammatory responses, immune regulation and cell survival, and its aberrant activation is a hallmark of numerous types of cancer (71). Ubiquitination plays dual roles in regulating both the canonical and non-canonical NF-κB pathways, with E3 ligases and DUBs acting as reciprocal regulators to maintain signaling homeostasis or drive oncogenic dysregulation (72). Specifically, ubiquitin ligases regulate NF-κB activation through distinct ubiquitination modes: K48-associated polyubiquitination mediates proteasomal degradation of inhibitory molecules, whereas K63-associated or M1-associated linear polyubiquitination serves as a non-degradative scaffold to support signaling complex assembly (73,74). In the canonical pathway, tumor necrosis factor receptor-associated factors (TRAFs), particularly TRAF6, act as key ubiquitin ligases that catalyze K63-associated ubiquitination of themselves and downstream kinases including TAK1 and the IKK complex, thereby recruiting ubiquitin-binding adaptors and activating the kinase cascade (75).

Modulation of PI3K-AKT signaling pathway by E3 ligases and DUBs. The PI3K-AKT signaling pathway serves as a core oncogenic cascade governing cell growth, survival, metabolism and angiogenesis, and its hyperactivation represents one of the most frequent alterations in human cancer (76). E3 ligases and DUBs tightly control this pathway by targeting key components, including PI3K, AKT, PTEN (a major negative regulator) and mTOR, to modulate their stability and activity (77,78).

For example, MDM2, a well-characterized E3 ubiquitin ligase, negatively regulates AKT signaling by targeting AKT for K48-associated ubiquitination and proteasomal degradation. Notably, its oncogenic activity is more commonly attributed to promoting the degradation of p53 (79). On the contrary, tumor-suppressive E3 ligases, such as RNF43 and CHIP, inhibit PI3K-AKT signaling by targeting oncogenic components: RNF43 mediates the degradation of B-RAF (a downstream effector of PI3K-AKT), while CHIP promotes PTEN stability by ubiquitinating and degrading PTEN-targeting E3 ligases (80,81). Furthermore, TRAF6 functions as a positive regulator by catalyzing K63-associated ubiquitination of AKT, which promotes AKT recruitment to the plasma membrane and its subsequent phosphorylation by 3'-phosphoinositide-dependent kinase (PDK)-1 and mTORC2, thereby augmenting its kinase activity (82).

6. Molecular mechanisms and functional consequences of ubiquitin-m^{6}A crosstalk

Ubiquitination, a PTM regulating protein fate, and m^{6}A which is the most abundant internal post-transcriptional modification of eukaryotic RNAs, constitute two core epigenetic regulatory systems that orchestrate gene expression programs in both physiological and pathological processes, especially during tumorigenesis (83,84). The crosstalk between these two modifications constructs a complex, multi-layered regulatory network that functions at the protein, RNA and chromatin levels.

Ubiquitin-m^{6}A crosstalk at the protein level. At the protein level, crosstalk is primarily defined by reciprocal regulation between the ubiquitination machinery (E3 ligases and DUBs) and m^{6}A regulators (writers, readers and erasers) (85,86). This reciprocal interplay fine-tunes the abundance and activity of m^{6}A modifiers, thereby indirectly shaping the global m^{6}A landscape and governing the downstream RNA metabolism (87).

Ubiquitination directly modulates the stability of m^{6}A writers, the core components responsible for m^{6}A deposition (88). For instance, METTL14, a core subunit of the m^{6}A

methyltransferase and a key determinant of cellular m^{6}A homeostasis, is precisely targeted by the E3 ubiquitin ligase STUB1. STUB1 catalyzes K48-associated polyubiquitination at lysine residues K148, K156 and K162 of METTL14, thereby promoting its proteasomal degradation (88,89). Notably, METTL3, another core writer subunit, competes with STUB1 for binding to METTL14, thus shielding METTL14 from ubiquitin-dependent degradation and preserving m^{6}A homeostasis in cells (90). Dysregulation of the METTL3-STUB1-METTL14 axis disturbs m^{6}A equilibrium and drives malignant progression, highlighting the therapeutic potential of targeting STUB1 to modulate METTL14 ubiquitination and cellular m^{6}A levels. Furthermore, the m^{6}A writer METTL3 is itself regulated by PTMs. SUMOylation, a modification associated with ubiquitination, occurs at its lysine residues and represses its m^{6}A methyltransferase activity; additional ubiquitination events, which remain incompletely characterized, might further fine-tune its function (91).

Conversely, m^{6}A modification indirectly governs the ubiquitination machinery by modulating the expression or activity of E3 ligases and DUBs. For example, the m^{6}A reader YTHDF2, whose expression is upregulated by melatonin in ovarian cells, enhances the expression of E3 ligase Ubiquitin-conjugating enzyme (UBE)3C via m^{6}A-dependent regulation (92). UBE3C subsequently catalyzes the polyubiquitination and degradation of the senescence-related protein p53, thereby attenuating ovarian aging and potentially influencing the survival of tumor cells (93). This YTHDF2/m^{6}A/UBE3C/P53 axis illustrates how m^{6}A readers associate RNA modification to protein ubiquitination, thereby directing cellular fate decisions.

Ubiquitin-m^{6}A crosstalk at the RNA level. At the RNA level, ubiquitination and m^{6}A modification converge to regulate RNA metabolism, including mRNA stability, translation, splicing and nuclear export (94). This crosstalk is mainly mediated either by m^{6}A readers that recruit ubiquitination machinery to target RNAs, or by ubiquitination of RNA-binding proteins that modulate their interaction with m^{6}A-modified RNAs.

A key mechanism involves m^{6}A readers serving as adaptors that bridge m^{6}A-modified RNAs to E3 ubiquitin ligases, thereby promoting the ubiquitination and degradation of target RNAs or their associated proteins. For example, in acute myeloid leukemia (AML), the m^{6}A writer METTL3 mediates m^{6}A modification of *FOXO3* mRNA, enhancing its stability and expression (95). Subsequently, the expressed protein FOXO3 regulates autophagy, promoting AML cell proliferation and resistance to anthracycline chemotherapy. The stability of m^{6}A-modified *FOXO3* mRNA is tightly controlled by a balance between m^{6}A-mediated stabilization and potential ubiquitination of RNA-bound proteins that regulate its turnover. Similarly, the m^{6}A reader YTHDF2 binds to m^{6}A-modified RNAs and recruits the CCR4-NOT deadenylase complex, which may be further regulated by ubiquitination to modulate mRNA degradation efficiency (96).

Ubiquitination of m^{6}A readers and/or erasers also modulates their ability to interact with m^{6}A-modified RNAs. For instance, ubiquitination of the m^{6}A eraser ALKBH5 by E3 ligases (for example, RNF130) regulates its sub-cellular localization and RNA-binding activity, thereby altering the global m^{6}A levels and impacting RNA splicing and translation. Moreover, in gastric cancer, METTL3-mediated m^{6}A modification of RAB27A mRNA promotes its expression, thereby enhancing exosome biogenesis (97). These exosomes, enriched in miRNA-17-92 clusters, reshape the peritoneal immune microenvironment to facilitate tumor metastasis (97), highlighting the downstream oncogenic consequences of RNA-level ubiquitin-m^{6}A crosstalk.

Ubiquitin-m^{6}A crosstalk at the chromatin level. At the chromatin level, ubiquitin-m^{6}A crosstalk regulates transcriptional dynamics and chromatin structure by coordinating histone ubiquitination, m^{6}A modification of chromatin-associated RNAs (caRNAs), and the recruitment of epigenetic regulatory complexes (98). This layer of crosstalk directly influences gene transcription, particularly oncogenes and tumor suppressors, by shaping chromatin accessibility and transcriptional elongation.

A striking example is the co-transcriptional regulation of m^{6}A modification governed by chromatin-associated ubiquitination cascades. The DEAD-box helicase DDX21 associates with the m^{6}A writer complex (METTL3/METTL14/WTAP) and colocalizes with R-loops (DNA-RNA hybrid structures) at chromatin regions (99). DDX21, whose enzymatic activity can be modulated by ubiquitination, facilitates the recruitment of METTL3 to chromatin, thereby promoting co-transcriptional m^{6}A modification on caRNAs (100). In turn, such m^{6}A marks recruit the reader protein YTHDC1, which enhances XRN2-mediated transcription termination and preserves genome stability. Dysregulation of this R-loop-DDX21-METTL3-m^{6}A regulatory axis disrupts transcriptional homeostasis and compromises genome integrity, ultimately driving tumorigenesis.

In addition, m^{6}A modification of ncRNAs involved in chromatin regulation is capable of modulating histone ubiquitination. For example, in Arabidopsis, m^{6}A modification of retrotransposon RNAs recruits m^{6}A readers (CPSF30-L and ECT12), which in turn recruit histone methyltransferases to promote inhibitory histone modifications (H3K9me2 and H3K27me1), silencing retrotransposon transcription and maintaining chromatin stability (101). While this mechanism is well-characterized in plants, emerging evidence suggests the existence of similar crosstalk in mammalian cells, where m^{6}A-modified ncRNAs regulate histone ubiquitination and chromatin state to regulate the expression of oncogenes.

Downstream effects on oncogenic signaling. Crosstalk between ubiquitination and m^{6}A RNA modification is key in modulating oncogenic signaling pathways (102). Primarily, m^{6}A marks regulate the stability, splicing, translation and localization of mRNAs encoding oncogenes or tumor suppressors, thereby modulating signaling activity at the post-transcriptional level (103). On the contrary, components of the ubiquitination machinery control the protein stability, abundance and sub-cellular distribution of m^{6}A writers, erasers and readers, leading to dynamic changes in the global m^{6}A landscape and influencing downstream pathway outputs (87). In addition, m^{6}A modification is also able to affect the expression or activity of E3 ubiquitin ligases and deubiquitinases, creating reciprocal feedback loops that fine-tune signaling

strength. Studies showed that the m^{6}A eraser FTO impaired gemcitabine resistance in pancreatic cancer by influencing the stability of NEDD4 mRNA through regulation of the PTEN/PI3K-AKT pathway (104). TRIM17, a member of the TRIM family with E3 ligase activity, has recently been implicated in the progression of various tumors, particularly in promoting cancer cell clonogenicity, survival and drug resistance (105). TRIM17 promotes the ubiquitination and degradation of FTO, enhances PDK1 mRNA stability via m^{6}A modification, and subsequently facilitates phosphorylation-dependent activation of the AKT/mTOR signaling pathway, thereby driving osteosarcoma progression (12). UBE2C is also involved in tumorigenesis, and studies have revealed that METTL3 upregulates UBE2C expression through m^{6}A modification, activating the PI3K-AKT pathway and promoting the development of retinoblastoma (106,107). Ubiquitination and m^{6}A modifications can regulate the mTORC1/p70S6K signaling pathway, thereby contributing to docetaxel resistance and liver metastasis (108). Furthermore, TP53TG1 contains abundant m^{6}A modification sites, and the demethylase ALKBH5 reduces its stability and expression (109). TP53TG1 interacts with cancerous inhibitor of protein phosphatase 2A and triggers its ubiquitin-mediated degradation, leading to inhibition of the PI3K-AKT pathway in gastric cancer (109).

7. Conclusions and perspectives

Ubiquitination and m^{6}A RNA methylation have emerged as two highly dynamic and interconnected regulatory systems shaping almost every aspect of cancer biology (110). Accumulating evidence demonstrates the interactions of the two pathways: They converge to modulate the stability, localization and activity of key oncogenic signaling proteins and RNAs (111). Through multilayered crosstalk, the two pathways jointly influence hallmark cancer processes, including proliferation, stemness, metabolic reprogramming, immune evasion and therapeutic resistance (112). Based on the existing evidence, the present review advances the field in several important ways. The multi-layered crosstalk between ubiquitination and m^{6}A modification at the protein, RNA and chromatin levels is systematically summarized, and how these two regulatory systems converge on core oncogenic signaling pathways to cooperatively modulate tumor cell proliferation, metastasis, metabolic reprogramming and therapeutic resistance has also been discussed. In addition, the present review highlights the context-dependent nature of ubiquitin-m^{6}A crosstalk and identifies key regulatory nodes with diagnostic and therapeutic potential. By providing a unified conceptual framework, the present review deepens mechanistic knowledge of cancer signaling networks and offers clear directions for the development of novel targeted strategies and combination therapies in precision oncology.

Unfortunately, current understanding remains fragmented. To date, the majority of studies have focused on individual molecules or pathways, leaving the broader regulatory network largely uncharacterized (113,114). The context-dependent roles of m^{6}A and ubiquitination further complicate interpretations, as the same enzyme can act as either an oncogene or a tumor suppressor, depending on the tumor type or micro-environment. In addition, how these pathways integrate signals from stress, inflammation and metabolism to rewire oncogenic circuits remains largely defined.

The bidirectional interplay between ubiquitination and m^{6}A modification provides a strong rationale for combination therapies, such as PROTACs combined with m^{6}A inhibitors. PROTACs leverage E3 ligases to induce targeted degradation of oncogenic proteins, while m^{6}A inhibitors (for example, METTL3 inhibitors and YTHDF2 inhibitors such as DC-Y13-27) disrupt m^{6}A-dependent RNA metabolism. Combining these agents yields synergistic effects by simultaneously targeting the ubiquitin-m^{6}A network at both the protein and RNA levels: For example, PROTACs directed against oncogenic E3 ligases (such as STUB1) can restore the stability of METTL14, while m^{6}A inhibitors further normalize m^{6}A modification profiles, collectively reversing the dysregulation of oncogenic signaling pathways. For instance, co-targeting the m^{6}A writer METTL3 and the E3 ligase STUB1 represents a rational dual-modulation strategy: STUB1 inhibition blocks METTL14 ubiquitination and degradation to restore m^{6}A homeostasis, while METTL3 inhibitors correct aberrant m^{6}A landscapes, thereby synergistically reversing oncogenic signaling hyperactivation (88,89).

In addition, combining YTHDF2 inhibitors with radiotherapy or immunotherapy enhances anti-tumor efficacy by overcoming myeloid-derived suppressor cells-induced immune suppression, highlighting the translational potential of targeting ubiquitin-m^{6}A crosstalk in combination regimens. Key translational challenges remain substantial: First, off-target effects are prevalent due to the pleiotropic and ubiquitous functions of ubiquitin and m^{6}A regulators; second, strong context specificity means the same target may exert opposing oncogenic or tumor-suppressive effects across cancer types; third, several small-molecule inhibitors targeting E3 ligases, DUBs and m^{6}A modifiers show poor solubility and bioavailability, which compromise *in vivo* delivery and therapeutic efficacy (3,50,115).

Other limitations also exist. Firstly, current understanding of ubiquitin-m^{6}A crosstalk remains largely molecule- or pathway-specific rather than systematic and the strong context specificity of regulatory axes has not been fully categorized. Secondly, although to summarize the compiling key regulators, signaling pathways and cancer types, as well as a focused discussion on biomarkers and combination therapies would provide a clearer reference, the present review prioritizes mechanistic dissection over large-scale summary and clinical translation. Moreover, several areas warrant further in-depth investigation. Systematic mapping of ubiquitination-m^{6}A crosstalk across diverse cancer types and single-cell contexts holds great potential to uncover novel regulatory nodes and clinically relevant biomarkers (116). Structural and biochemical analyses are imperative to elucidate how ubiquitination modulates the m^{6}A regulatory machinery and how m^{6}A modification, in turn, reciprocally affects ubiquitination processes. Expanding research efforts into the roles of such crosstalk in immune regulation and the tumor micro-environment may reveal previously unrecognized links that are key to immunotherapy response. From a therapeutic perspective, targeting the interplay between these two pathways represents a highly promising direction for anticancer drug development. Dual-modulation strategies, selective degraders and

inhibitors targeting specific enzyme interfaces are expected to yield next-generation anticancer agents with enhanced precision and diminished off-target toxicity (117).

In summary, the convergence of ubiquitination and m^{6}A modification constitutes a fundamental layer of post-transcriptional and post-translational regulation in cancer. Deciphering their integrated regulatory networks will not only deepen the current understanding of tumor biology but also pave new avenues for the innovation of diagnostic strategies and therapeutic interventions.

Acknowledgements

Not applicable.

Funding

The study was supported by grants from the Wings Scientific and Technological Foundation of The First People's Hospital of Changde City (grant no. 2025ZC04) and the Changde City Science and Technology Innovation Guidance Plan Project (grant no. 2025ZD245).

Availability of data and materials

Not applicable.

Authors' contributions

HL drafted the original manuscript. XL supervised the project and revised the manuscript critically. Data authentication is not applicable. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Pan S and Chen R: Pathological implication of protein post-translational modifications in cancer. Mol Aspects Med 86: 101097, 2022.
2. Liu F, Chen J, Li K, Li H, Zhu Y, Zhai Y, Lu B, Fan Y, Liu Z, Chen X, *et al*: Ubiquitination and deubiquitination in cancer: From mechanisms to novel therapeutic approaches. Mol Cancer 23: 148, 2024.
3. Dagar G, Kumar R, Yadav KK, Singh M and Pandita TK: Ubiquitination and deubiquitination: Implications on cancer therapy. Biochim Biophys Acta Gene Regul Mech 1866: 194979, 2023.
4. Liu J, Zhang C, Xu D, Zhang T, Chang CY, Wang J, Liu J, Zhang L, Haffty BG, Zong WX, *et al*: The ubiquitin ligase TRIM21 regulates mutant p53 accumulation and gain of function in cancer. J Clin Invest 133: e164354, 2023.
5. Dewson G, Eichhorn PJA and Komander D: Deubiquitinases in cancer. Nat Rev Cancer 23: 842-862, 2023.
6. Fu X, Ruan X and He J: METTL3-driven m^{6}A epigenetics in gastric cancer: Unveiling oncogenic networks and clinical translation from tumorigenesis to therapy resistance. Cell Biol Toxicol 41: 132, 2025.
7. An Y and Duan H: The role of m6A RNA methylation in cancer metabolism. Mol Cancer 21: 14, 2022.
8. Cai M, Li X, Luan X, Zhao P and Sun Q: Exploring m6A methylation in skin cancer: Insights into molecular mechanisms and treatment. Cell Signal 124: 111420, 2024.
9. Li Q, Huang X, Tong Y, Yong C, Song M, Chang C, Dong H, Bu F, Yan S, Ying J and Chen J: N6-Methyladenosine-modified circNEK11 promotes hepatocellular carcinoma progression via the miR-1236-3p/GPX2 axis. Cancer Sci 116: 3326-3336, 2025.
10. Yin H, Zhang X, Yang P, Zhang X, Peng Y, Li D, Yu Y, Wu Y, Wang Y, Zhang J, *et al*: RNA m6A methylation orchestrates cancer growth and metastasis via macrophage reprogramming. Nat Commun 12: 1394, 2021.
11. Qian Y, Wang H, Feng Y, Zhang Y, Hu Q, Pan Z, Zhang X, Xu L, Yin L, Dong G, *et al*: The N6-methyladenosine-mediated cLMNB1 degrades FGFR4 to overcome osimertinib resistance in non-small cell lung cancer. Cell Death Dis 16: 818, 2025.
12. Liu W, Zheng D, Huang X, Wei Z, Wei Z and Guo W: TRIM17 promotes the progression of osteosarcoma by regulating PDK1 m6A modification-mediated AKT/mTOR pathway activation through ubiquitination of FTO. Cell Death Dis 16: 767, 2025.
13. Zhang X, Zhu C, Huang B and Wang H: The dual-edged sword: AlkB homolog 5-mediated autophagy regulation in cancers-molecular mechanisms and therapeutic implications: A review. Int J Biol Macromol 321 (Pt 1): 146227, 2025.
14. Yu L, Wei J and Liu P: Attacking the PI3K/Akt/mTOR signaling pathway for targeted therapeutic treatment in human cancer. Semin Cancer Biol 85: 69-94, 2022.
15. Zhou Y, Xu J, Luo H, Meng X, Chen M and Zhu D: Wnt signaling pathway in cancer immunotherapy. Cancer Lett 525: 84-96, 2022.
16. Su Y, Yang G, Chen B, Qian Y, Ma W, Jiang X, Yu Q, Li Y and Xu L: Enhancement of CAR-T cell efficacy and persistence via CD30 costimulation and NF-κB signaling. Mol Cancer 24: 289, 2025.
17. Han D, Wang L, Jiang S and Yang Q: The ubiquitin-proteasome system in breast cancer. Trends Mol Med 29: 599-621, 2023.
18. Zhou F, Li X, Sun Y, Wang Y, Niu K, Gao X, Zhang J, Chen T, Li Y, Zhao W, *et al*: USP39 at the crossroads of cancer immunity: Regulating immune evasion and immunotherapy response through RNA splicing and ubiquitin signaling. Front Immunol 16: 1665775, 2025.
19. Liu Z, Lai J, Ma Z, Pan J, Yang C and Fu R: Targeting the ubiquitin-proteasome system for cancer. MedComm (2020) 6: e70391, 2025.
20. Koo SY, Park EJ, Noh HJ, Jo SM, Ko BK, Shin HJ and Lee CW: Ubiquitination links DNA damage and repair signaling to cancer metabolism. Int J Mol Sci 24: 8441, 2023.
21. Zhao X, Li M, Fu Y, Chen C, Chen Y, Xu L, Bao L, Ma Z, Xu J, Zhou S, *et al*: PSMD14-mediated PFKFB2 deubiquitination activates H3K27 lactylation to drive cancer stemness in gastric adenocarcinoma. Cell Death Differ 33: 813-830, 2026.
22. Chen D, Zhao Y, Zhang X, Shi X, Liu Y and Lou G: USP33-mediated stabilization of c-Myc drives glycolytic reprogramming and promotes ovarian cancer progression. Biochim Biophys Acta Gen Subj 1869: 130830, 2025.
23. Zhang R, Shen Y, Zhang Q, Feng X, Liu X, Huo X, Sun J and Hao J: TRIM21-mediated Sohlh2 ubiquitination suppresses M2 macrophage polarization and progression of triple-negative breast cancer. Cell Death Dis 14: 850, 2023.
24. Li W, Liang L, Liu S, Tang J, Ou S, Yuan Z, Zhou Y and Yuan X: Inhibin beta A drives colorectal cancer progression through macrophage M2 polarization and mitochondria-dependent ferroptosis suppression. Signal Transduct Target Ther 10: 420, 2025.
25. Chen WJ, Chen LH, Wang J, Wang ZT, Wu CY, Sun K, Ding BY, Liu N and Xu RX: LHPP impedes energy metabolism by inducing ubiquitin-mediated degradation of PKM2 in glioblastoma. Am J Cancer Res 11: 1369-1390, 2021.
26. Li YT, Li KY, Tao SS, Wang T, Lu Y, Chen H, Zhan YQ, Zhao K, Xiang SS, Li JJ, *et al*: USP13 stabilizes NLRP3 to facilitate inflammasome activation by preventing TRIM31-mediated NLRP3 ubiquitination and degradation. Sci Adv 11: eadx3827, 2025.

27. Liu W, Zhou L, Le Y, He Y, Zhou J, Zhang H, Zhan J, Hu T, Wang J, Lin Y, *et al*: UCHL3 depletion inhibits gastric cancer progression and enhances palbociclib sensitivity by regulating the AKT/CCND1 signaling axis via ENO1 ubiquitination. Cell Death Dis 16: 850, 2025.
28. Li X, Pu W, Zheng Q, Ai M, Chen S and Peng Y: Proteolysis-targeting chimeras (PROTACs) in cancer therapy. Mol Cancer 21: 99, 2022.
29. Li Z, Wang Z, Zhong C, Zhang H, Liu R, An P, Ma Z, Lu J, Pan C, Zhang Z, *et al*: P53 upregulation by USP7-engaging molecular glues. Sci Bull (Beijing) 69: 1936-1953, 2024.
30. Guenette RG, Yang SW, Min J, Pei B and Potts PR: Target and tissue selectivity of PROTAC degraders. Chem Soc Rev 51: 5740-5756, 2022.
31. Snyder LB, Neklesa TK, Willard RR, Gordon DA, Pizzano J, Vitale N, Robling K, Dorso MA, Moghrabi W, Landrette S, *et al*: Preclinical evaluation of bavdegalutamide (ARV-110), a novel PROteolysis TArgeting chimera androgen receptor degrader. Mol Cancer Ther 24: 511-522, 2025.
32. Gough SM, Flanagan JJ, The J, Andreoli M, Rousseau E, Pannone M, Bookbinder M, Willard R, Davenport K, Bortolon E, *et al*: Oral estrogen receptor PROTAC Vepdegestrant (ARV-471) Is highly efficacious as monotherapy and in combination with CDK4/6 or PI3K/mTOR pathway inhibitors in preclinical ER+ Breast cancer models. Clin Cancer Res 30: 3549-3563, 2024.
33. Dai XS, Dong B, Xu L and Yang ZM: Synthesis of two versions of carbon-14-labeled ARV-110: An androgen receptor PROTAC degrader for prostate cancer. J Labelled Comp Radiopharm 68: e4154, 2025.
34. Basnet J, Rezq S, Huffman AM, Asala TE, Yanes Cardozo LL and Romero DG: Androgen receptor PROTAC ARV-110 ameliorates metabolic complications in a mouse model of polycystic ovary syndrome. Endocrinology 166: bqaf091, 2025.
35. Zammit CM, Nadel CM, Lin Y, Koirala S, Ahani E, Potts PR and Nomura DK: Covalent destabilizing degrader of AR and AR-V7 in androgen-independent prostate cancer cells. J Am Chem Soc 147: 20512-20524, 2025.
36. Ferrero JM, Gal J, Mograbi B and Milano G: PROTACs and glues: Striking perspectives for engineering cancer therapy À La Carte. Pharmaceuticals (Basel) 18: 1397, 2025.
37. Surka C, Jin L, Mbong N, Lu CC, Jang IS, Rychak E, Mendy D, Clayton T, Tindall E, Hsu C, *et al*: CC-90009, a novel cereblon E3 ligase modulator, targets acute myeloid leukemia blasts and leukemia stem cells. Blood 137: 661-677, 2021.
38. Zuo X, Liu G, Guo J and Wang Y: Unveiling the role of m6A modification in esophageal cancer: A new frontier in tumor innate interferon immunity. Cancer Cell Int 25: 412, 2025.
39. Chen YN, Zhu S, Sun LJ, Zhou RR, Zheng R, Li XF, Li LY, Sun SJ, Zhao YX, Huang C, *et al*: Unveiling the dynamics and therapeutic potential of m(6)A methyltransferases and demethylases in liver diseases. Int J Biol Sci 21: 6252-6269, 2025.
40. Zhou Y, Corovic M, Hoch-Kraft P, Meiser N, Mesitov M, Körtel N, Back H, Naarmann-de Vries IS, Katti K, Obrdlík A, *et al*: m6A sites in the coding region trigger translation-dependent mRNA decay. Mol Cell 84: 4576-4593 e12, 2024.
41. Jiang HT, Qian SY, Di PR, Jin CC and Pu QH: Hypoxia-mediated m(6)A modulation in hepatocellular carcinoma: A comprehensive review. J Transl Med 23: 1216, 2025.
42. Wang X, Zhao BS, Roundtree IA, Lu Z, Han D, Ma H, Weng X, Chen K, Shi H and He C: N(6)-methyladenosine modulates messenger RNA translation efficiency. Cell 161: 1388-1399, 2015.
43. Yuan F, Zhang W, Xia Y, Zhou X and Gao H: The role and mechanism of METTL3 in cancer: Emerging insights into m6A methylation and therapeutic potential. Eur J Med Res 30: 1017, 2025.
44. Chen X, Pu S, Lian K, Li L and Jiang X: m6A RNA modification in tumor-associated macrophages: Emerging roles in cancer immunity. Front Immunol 16: 1693336, 2025.
45. Altalbawy F, Azzam ER, Alkhathami A, Hussn A, Malathi H, Bhatt A, Shankhyan A, Nayak PP, Almalki S and Alnajar MJ: Epitranscriptomic sculpting: The role of m(6)A in alternative splicing, cancer progression, and methodological insights. Med Oncol 42: 492, 2025.
46. Pádua D, Mesquita P and Almeida R: The epitranscriptomic landscape of gastric cancer stem cells: The emerging role of m(6) A RNA modifications. Cancers (Basel) 17: 3589, 2025.
47. Chen Z, Hu Y, Jin L, Yang F, Ding H, Zhang L, Li L and Pan T: The emerging role of N6-methyladenosine RNA methylation as regulators in cancer therapy and drug resistance. Front Pharmacol 13: 873030, 2022.
48. Lu S, Liu J, Chen S, Li B and Ye Z: M(6)A methylation in tumor immune microenvironment: Multidimensional mechanism and targeted therapy strategies. Biochim Biophys Acta Rev Cancer 1880: 189489, 2025.
49. Wang YF, Wang ZH, Zhang ZC, Tan J, Li ZX, Yin HZ, Piao XJ, Dai ZH, Mu CY, Wang SJ, *et al*: YTHDF1 regulates YTHDF2 stability via m6A-dependent mechanisms in hepatocellular carcinoma: Insights from in vitro, in vivo, and multi-cohort clinical studies. J Gastrointest Oncol 16: 2225-2244, 2025.
50. He PC and He C: m(6) A RNA methylation: From mechanisms to therapeutic potential. EMBO J 40: e105977, 2021.
51. Sun M, Wang M, Gao H, Li L, Wu M, Li Q, Bu F, Dong H, Han J, Ying J and Chen J: The interplay between post-transcriptional RNA regulation and Wnt/β-Catenin signaling in cancer: A Review. Int J Biol Macromol 328 (Pt 2): 147657, 2025.
52. Qin S, Mao Y, Wang H, Duan Y and Zhao L: The interplay between m6A modification and non-coding RNA in cancer stemness modulation: Mechanisms, signaling pathways, and clinical implications. Int J Biol Sci 17: 2718-2736, 2021.
53. Wu F, Yang J, Liu J, Wang Y, Mu J, Zeng Q, Deng S and Zhou H: Signaling pathways in cancer-associated fibroblasts and targeted therapy for cancer. Signal Transduct Target Ther 6: 218, 2021.
54. Liu L, Wang R, Cheng K, Bai C, Ji Y, Zhang Y, Yang H, Gong M, Xie F, Zhao Y, *et al*: Steroid receptor coactivator-1 facilitates METTL3-mediated m6A modification by coactivating NF-κB and promotes the malignant progression of glioblastoma. Oncogene 44: 3333-3349, 2025.
55. Wei J, Zhao X, Wang H, Wang C, Liu X, Shan Z, Guo Y, Gu X, Li R and Zhu Z: STAT1 and m(6)A-mediated IL15RA upregulation promotes metastasis via ZEB1/NF-κB axis in ccRCC. Sci Rep 15: 37990, 2025.
56. Chun H and Baima K: Unraveling the dual role of METTL3-mediated m(6)A RNA modification in bladder cancer: Mechanisms, therapeutic vulnerabilities, and clinical implications. Cancer Biol Ther 26: 2545057, 2025.
57. Wu J, Liu L, Xu B, Wang R, Ma W and Deng J: FTO enhances OSCC progression via m^{6}A-dependent stabilization of PKM2 mRNA through YTHDF2 modulation. Head Face Med 21: 71, 2025.
58. Cheng M, Sheng L, Gao Q, Xiong Q, Zhang H, Wu M, Liang Y, Zhu F, Zhang Y, Zhang X, *et al*: The m(6)A methyltransferase METTL3 promotes bladder cancer progression via AFF4/NF-κB/MYC signaling network. Oncogene 38: 3667-3680, 2019.
59. Wang J, Tan L, Jia B, Yu X, Yao R, OUYang N, Yu X, Cao X, Tong J, Chen T, *et al*: Downregulation of m(6)A reader YTHDC2 promotes the proliferation and migration of malignant lung cells via CYLD/NF-κB pathway. Int J Biol Sci 17: 2633-2651, 2021.
60. He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW and Li B: Targeting PI3K/Akt signal transduction for cancer therapy. Signal Transduct Target Ther 6: 425, 2021.
61. Zang S, Ouyang Y, Li P and Yin X: Hypothalamic FTO upregulates BDNF to promote GnRH expression through the PI3K/Akt pathway, leading to precocious puberty. Front Endocrinol (Lausanne) 16: 1665391, 2025.
62. Chen X, Xu M, Xu X, Zeng K, Liu X, Pan B, Li C, Sun L, Qin J, Xu T, *et al*: METTL14-mediated N6-methyladenosine modification of SOX4 mRNA inhibits tumor metastasis in colorectal cancer. Mol Cancer 19: 106, 2020.
63. Li P, Shi Y, Gao D, Xu H, Zou Y, Wang Z and Li W: ELK1-mediated YTHDF1 drives prostate cancer progression by facilitating the translation of Polo-like kinase 1 in an m6A dependent manner. Int J Biol Sci 18: 6145-6162, 2022.
64. Li Y, Huang Z, Huang X, Lin W, Ding Q, Fu W, Chen R, Lai J, Wang J, Liu Q and Qiu S: PXDN regulated by WTAP/YTHDF1-mediated m(6)A modification activates PI3K/AKT signaling pathway through extracellular matrix remodeling to promote progression in nasopharyngeal carcinoma. J Exp Clin Cancer Res 45: 21, 2025.
65. Yi Q, Zhong K, Chen Z, Ouyang X, Zhu W, Liang L and Zhong J: m^{6}A-modified circMELK regulates nasopharyngeal carcinoma progression via a YTHDF1/circMELK-miR-4775-HMGA2 feedback loop. Mol Immunol 193: 50-67, 2026.
66. Wang P, Chen S, Lei M, Chen Y, He H, Chen P, Chen W, Zhou H, Wang F and Zhang D: METTL3-mediated m6A methylation of LncRNA DUXAP8 promoted esophageal squamous cell carcinoma progression by activating the PI3K/AKT signaling pathway. Cell Div 21: 1, 2025.

67. Qin S, Chen K, Chen S, Chen X, Hu Y, Peng W, Pan Z, Ji X, Pang P, Luo Q and Liu W: N6-methyladenosine-modified circDCP2 promotes carbon black nanoparticle-induced malignancy in human bronchial epithelial cells via PI3K-AKT pathway and macrophage homeostasis. J Nanobiotechnology 23: 555, 2025.
68. Lai S, Yu L, Sun L, Zheng H, Lu T, Li Z, Chen C, Wei Y and Wen W: Integrated m6A methylome and transcriptome profiling of mRNAs and lncRNAs in nasal mucosal epithelial cells of allergic rhinitis patients undergoing allergen-specific immunotherapy. Clin Epigenetics: Apr 19, 2026 (Epub ahead of print).
69. Singhal C, Upadhyaya G, Rajkumar MS, Modak A, Sethi V, Singh S, Das D, Jain M and Gangappa SN: CUL3(LRB) E3 ubiquitin ligases control thermosensory growth in Arabidopsis by differentially regulating HY5 and PIF4 protein stability. Sci Adv 12: eaec7817, 2026.
70. Collotta G, Gatti M, Ungureanu IM, van Ackeren V, Rannou E, Vivalda F, Gomez Vieito D, Fishwick KM, von Aesch C, Porro A, *et al*: USP7 deubiquitinase stabilizes FAN1 to support DNA crosslink repair and suppress CAG repeat expansion. Nat Commun 17: 3551, 2026.
71. Ulianova YA, Ghassah M, Kachaev ZM, Lebedeva LA and Shidlovskii YV: The conserved network of NF-κB transcriptional partners from drosophila to mammals. J Mol Biol 438: 169572, 2026.
72. Xiao Y, Lei Y, He Q, Zeng T and Ling H: Mechanistic insights and therapeutic potential of E3 ubiquitin ligases in gastric cancer development. Biochem Biophys Res Commun 803: 153340, 2026.
73. Wei CH, Weng CW, Wu CY, Chen HY, Chang YH, Chang GC and Chen JJW: E3 ligase TRIM8 suppresses lung cancer metastasis by targeting MYOF degradation through K48-linked polyubiquitination. Cell Death Dis 16: 88, 2025.
74. Gao L, Zhang W, Shi XH, Chang X, Han Y, Liu C, Jiang Z and Yang X: The mechanism of linear ubiquitination in regulating cell death and correlative diseases. Cell Death Dis 14: 659, 2023.
75. Strickson S, Emmerich CH, Goh ETH, Zhang J, Kelsall IR, Macartney T, Hastie CJ, Knebel A, Peggie M, Marchesi F, *et al*: Roles of the TRAF6 and Pellino E3 ligases in MyD88 and RANKL signaling. Proc Natl Acad Sci USA 114: E3481-e3489, 2017.
76. Fontana F, Giannitti G, Marchesi S and Limonta P: The PI3K/Akt pathway and glucose metabolism: A dangerous liaison in cancer. Int J Biol Sci 20: 3113-3125, 2024.
77. Wang W, Shi B, Cong R, Hao M, Peng Y, Yang H, Song J, Feng D, Zhang N and Li D: RING-finger E3 ligases regulatory network in PI3K/AKT-mediated glucose metabolism. Cell Death Discov 8: 372, 2022.
78. Wang K, Liu J, Li YL, Li JP and Zhang R: Ubiquitination/de-ubiquitination: A promising therapeutic target for PTEN reactivation in cancer. Biochim Biophys Acta Rev Cancer 1877: 188723, 2022.
79. Guo Y, Li Q, Zhao G, Zhang J, Yuan H, Feng T, Ou D, Gu R, Li S, Li K and Lin P: Loss of TRIM31 promotes breast cancer progression through regulating K48- and K63-linked ubiquitination of p53. Cell Death Dis 12: 945, 2021.
80. Nag JK, Appasamy P, Malka H, Sedley S and Bar-Shavit R: New Target(s) for RNF43 regulation: Implications for therapeutic strategies. Int J Mol Sci 25: 8083, 2024.
81. Hsu SH, Tsai YL, Wang YT, Shen CH, Hung YH, Chen LT and Hung WC: RNF43 inactivation enhances the B-RAF/MEK signaling and creates a combinatory therapeutic target in cancer cells. Adv Sci (Weinh) 11: e2304820, 2024.
82. Wang YT, Liu TY, Shen CH, Lin SY, Hung CC, Hsu LC and Chen GC: K48/K63-linked polyubiquitination of ATG9A by TRAF6 E3 ligase regulates oxidative stress-induced autophagy. Cell Rep 38: 110354, 2022.
83. Zhou B, Luo Y, Bi H, Zhang N, Ma M, Dong Z, Ji N, Zhang S, Wang X, Liu Y, *et al*: Amelioration of nonalcoholic fatty liver disease by inhibiting the deubiquitylating enzyme RPN11. Cell Metab 36: 2228-2244.e7, 2024.
84. Shi Y, Liu B, Zhang Y, Zhao S, Zuo L, Pu J, Zhai H, Mu D, Du J, Cheng Y, *et al*: YTHDF1/RNF7/p27 axis promotes prostate cancer progression. Cell Death Dis 16: 314, 2025.
85. Ebadi P, Stratton CM and Olsen SK: E3 ubiquitin ligases in signaling, disease, and therapeutics. Trends Biochem Sci 50: 960-976, 2025.
86. Zhao L, Kang M, Liu X, Wang Z, Wang Y, Chen H, Liu W, Liu S, Li B, Li C, *et al*: UBR7 inhibits HCC tumorigenesis by targeting Keap1/Nrf2/Bach1/HK2 and glycolysis. J Exp Clin Cancer Res 41: 330, 2022.
87. Zhao Y, Huang J, Zhao K, Li M and Wang S: Ubiquitination and deubiquitination in the regulation of N(6)-methyladenosine functional molecules. J Mol Med (Berl) 102: 337-351, 2024.
88. Zeng ZC, Pan Q, Sun YM, Huang HJ, Chen XT, Chen TQ, He B, Ye H, Zhu SX, Pu KJ, *et al*: METTL3 protects METTL14 from STUB1-mediated degradation to maintain m(6) A homeostasis. EMBO Rep 24: e55762, 2023.
89. Han H, Li Z, Feng Y, Song H, Fang Z, Zhang D, Yuan D and Shi J: Peptide degrader-based targeting of METTL3/14 improves immunotherapy response in cutaneous melanoma. Angew Chem Int Ed Engl 63: e202407381, 2024.
90. Li Y, Luo B, Lin X, Bai D, Li L, Gao D, Li X, Zhong X, Wei Y, Yang L, *et al*: 20(R)-Panaxatriol enhances METTL3-mediated m(6)A modification of STUB1 to inhibit autophagy and exert antitumor effects in triple-negative breast cancer cells. Phytomedicine 130: 155537, 2024.
91. Du Y, Hou G, Zhang H, Dou J, He J, Guo Y, Li L, Chen R, Wang Y, Deng R, *et al*: SUMOylation of the m6A-RNA methyltransferase METTL3 modulates its function. Nucleic Acids Res 46: 5195-5208, 2018.
92. Xia W, Wang X, Li J, Zhang M, Lu J, Li H, He Q, Meng Q and Huang B: Melatonin mitigates ovarian aging through regulation of the YTHDF2/m (6)A/UBE3C axis. Acta Biochim Biophys Sin (Shanghai) 57: 1529-1538, 2025.
93. Shi Y, Wang J, Cheng Q, Wu S, Qin X and Yang Z: UBE3C promotes pancreatic ductal adenocarcinoma progression by catalysing p53 ubiquitination. Mol Biol Rep 52: 633, 2025.
94. Chen YG, Chen R, Ahmad S, Verma R, Kasturi SP, Amaya L, Broughton JP, Kim J, Cadena C, Pulendran B, *et al*: N6-Methyladenosine modification controls circular RNA Immunity. Mol Cell 76: 96-109.e9, 2019.
95. Zhang X, Yang J, Wen Y, Liu Q, Dou L and Gao C: METTL3-mediated m(6)A modification promotes FOXO3 expression and anthracycline resistance in acute myeloid leukemia cells through autophagy regulation. Nan Fang Yi Ke Da Xue Xue Bao 45: 470-478, 2025 (In Chinese).
96. Du H, Zhao Y, He J, Zhang Y, Xi H, Liu M, Ma J and Wu L: YTHDF2 destabilizes m(6)A-containing RNA through direct recruitment of the CCR4-NOT deadenylase complex. Nat Commun 7: 12626, 2016.
97. Li S, Zhou J, Wang S, Yang Q, Nie S, Ji C, Zhang X, Li S, Zhou X, Chu J, *et al*: N(6)-methyladenosine-regulated exosome biogenesis orchestrates an immunosuppressive pre-metastatic niche in gastric cancer peritoneal metastasis. Cancer Commun (Lond) 45: 941-965, 2025.
98. Huang X, Zhang J, Cun Y, Ye M, Ren Z, Guo W, Ma X, Liu J, Luo W, Sun X, *et al*: Spatial control of m(6)A deposition on enhancer and promoter RNAs through co-acetylation of METTL3 and H3K27 on chromatin. Mol Cell 85: 1349-1365.e10, 2025.
99. Lavergne G and Roignant JY: DDX21: The link between m(6)A and R-loops. Mol Cell 84: 1631-1632, 2024.
100. Zhao Y, Zhou Y, Qian Y, Wei W, Lin X, Mao S, Sun J and Jin J: m(6)A-dependent upregulation of DDX21 by super-enhancer-driven IGF2BP2 and IGF2BP3 facilitates progression of acute myeloid leukaemia. Clin Transl Med 14: e1628, 2024.
101. Li Y, Xia L, Tan K, Ye X, Zuo Z, Li M, Xiao R, Wang Z, Liu X, Deng M, *et al*: N(6)-Methyladenosine co-transcriptionally directs the demethylation of histone H3K9me2. Nat Genet 52: 870-877, 2020.
102. Lv S, Zhang J, Peng X, Liu H, Chu T, Liu Z, Duan K, Guo J, Wang J, Liu Y and Wei F: Hsa_circ_0058495-mediated IGF2BP2 ubiquitination and m6A modification of MEKK1 promote the progression of PDAC. Theranostics 15: 9922-9943, 2025.
103. Qiu Y, Man C, Zhu L, Zhang S, Wang X, Gong D and Fan Y: R-loops' m6A modification and its roles in cancers. Mol Cancer 23: 232, 2024.
104. Lin K, Zhou E, Shi T, Zhang S, Zhang J, Zheng Z, Pan Y, Gao W and Yu Y: m6A eraser FTO impairs gemcitabine resistance in pancreatic cancer through influencing NEDD4 mRNA stability by regulating the PTEN/PI3K/AKT pathway. J Exp Clin Cancer Res 42: 217, 2023.
105. Shen J, Yang H, Qiao X, Chen Y, Zheng L, Lin J, Lang J, Yu Q and Wang Z: The E3 ubiquitin ligase TRIM17 promotes gastric cancer survival and progression via controlling BAX stability and antagonizing apoptosis. Cell Death Differ 30: 2322-2335, 2023.

106. Chen L and Mei S: UBE2C, Regulated by n6-methyladenosine Methyltransferase METTL3, Is an oncogene in retinoblastoma via PI3K-AKT pathway. DNA Cell Biol 44: 436-444, 2025.
107. Zhang ZF, Lok CN and Che CM: Anti-cancer binuclear gold(I) complexes with mixed bis(N-heterocyclic carbene) and bis(diphenylphosphino)carborane ligands inhibit thioredoxin reductase and engage ubiquitin-conjugating enzyme E2 C UBE2C in lung cancer cells. J Inorg Biochem 281: 113324, 2026.
108. Ou X, Tan Y, Xie J, Yuan J, Deng X, Shao R, Song C, Cao X, Xie X, He R, *et al*: Methylation of GPRC5A promotes liver metastasis and docetaxel resistance through activating mTOR signaling pathway in triple negative breast cancer. Drug Resist Updat 73: 101063, 2024.
109. Fang D, Ou X, Sun K, Zhou X, Li Y, Shi P, Zhao Z, He Y, Peng J and Xu J: m6A modification-mediated lncRNA TP53TG1 inhibits gastric cancer progression by regulating CIP2A stability. Cancer Sci 113: 4135-4150, 2022.
110. Wang A, Huang H, Shi JH, Yu X, Ding R, Zhang Y, Han Q, Ni ZY, Li X, Zhao R and Zou Q: USP47 inhibits m6A-dependent c-Myc translation to maintain regulatory T cell metabolic and functional homeostasis. J Clin Invest 133: e169365, 2023.
111. Wang J, Xiu M, Wang J, Gao Y and Li Y: METTL16-SENP3-LTF axis confers ferroptosis resistance and facilitates tumorigenesis in hepatocellular carcinoma. J Hematol Oncol 17: 78, 2024.
112. Liang YL, Zhong CR, Wu JY, Lin ZJ, Lin Z, Yi TJ, Chen ZP, Jin HL, Yu JD, Lin ZY, *et al*: USP10 promotes cell proliferation and gemcitabine resistance in pancreatic cancer by the regulation of IGF2BP3-STEAP3. Oncogene 45: 383-397, 2026.
113. Zhang X, Zhang Y, Yang X, Fan Y and Zhu Y: Mechanism of YTHDF2-Mediated epigenetic modification in the proliferation and invasion of renal cell carcinoma cells. Biofactors 52: e70099, 2026.
114. Zhou B, Lin Z, Guo Y, Xin W, Ding J, Tang W and Zhang H: USP22 in human cancers: Mechanistic insights and inhibitor development. Eur J Med Chem 312: 118865, 2026.
115. Chen Y, Liu F, Pal S and Hu Q: Proteolysis-targeting drug delivery system (ProDDS): Integrating targeted protein degradation concepts into formulation design. Chem Soc Rev 53: 9582-9608, 2024.
116. You L, Wang Q, Zhang T, Xiao H, Lv M, Lv H, Deng L, Zhang X and Zhang Y: USP14-IMP2-CXCL2 axis in tumor-associated macrophages facilitates resistance to anti-PD-1 therapy in gastric cancer by recruiting myeloid-derived suppressor cells. Oncogene 44: 2413-2426, 2025.
117. Wang J, Guo X, Chen Y, Zhang W, Ren J and Gao A: RNA m6A reader YTHDF3/UBE2G2 m6A methylation/ACSL4 ubiquitination axis facilitated cell ferroptosis to mediate benzene hematotoxicity and the protective effect of melatonin. Ecotoxicol Environ Saf 305: 119257, 2025.