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m^{6}A modification in cancer regulation: molecular circuits and regulatory networks

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Abstract – The N6-methyladenosine (m^{6}A) modification is a significant research direction in the field of epitranscriptomics, and its multifaceted functions in tumor regulation have garnered increasing attention. Through the actions of three core enzyme groups, writers, erasers, and readers, m^{6}A modification dynamically regulates RNA stability, translation efficiency, and localization, thereby on·uancong biological processes in tumor cells, such as proliferation, metastasis, and drug resistance. This review outlines the m^{6}A modification's regulatory roles in tumor autophagy and apoptosis, metabolic reprogramming, and dynamic alterations within the tumor microenvironment. Specifically, it elaborates on how m^{6}A orchestrates microenvironmental remodeling to promote tumor progression through mechanisms including autophagy signaling transduction, apoptotic gene regulation, metabolic gene modulation, as well as functional reprogramming of immune cells and endothelial cells. Although significant progress has been made in m^{6}A-related tumor research, challenges remain, including its dynamic and reversible regulatory mechanisms, heterogeneity-driven functional differences, and clinical translation applications. Future studies should further explore the specific regulatory mechanisms of m^{6}A modification, develop targeted therapeutic strategies, and integrate multi-omics and artificial intelligence technologies to construct dynamic regulatory network models. These efforts will facilitate the translation of basic research findings into clinical applications, providing novel insights and strategies for tumor diagnosis and treatment.

Key words: Tumor, m^{6}A, Autophagy, Metabolism, Tumor microenvironment.

Introduction

As a pivotal component of epigenetic regulation, RNA modifications have emerged as critical mediators of gene expression control, with N6-methyladenosine (m^{6}A) representing the most prevalent internal post-transcriptional modification in eukaryotic mRNAs [1]. The m^{6}A modification, which refers to a methylation at the N6-position of adenosine, predominantly occurring in the 3'UTR region and RRACH ([G>A]m6AC [U>A>C]) sequence of RNA, is regulated by "writers" (methyltransferases), "erasers" (demethylases), and "readers" (RNA-binding proteins) [2]. This dynamic and reversible methylation process exerts multifaceted regulatory effects on RNA metabolism, including splicing, nuclear export, stability maintenance, and translational efficiency, thereby orchestrating cellular homeostasis [3]. Emerging evidence has elucidated the pivotal roles of RNA modifications, particularly m^{6}A, in tumorigenesis and cancer progression through diverse molecular mechanisms [4].

Current research demonstrates that m^{6}A dysregulation not only drives malignant transformation via canonical oncogenic pathways such as Wnt/β-catenin and PI3K/AKT/mTOR signaling [5, 6], but also coordinates critical biological processes including tumor autophagy and apoptosis [7, 8], metabolic reprogramming [9], immune evasion [10], and therapeutic resistance [11]. Mechanistically, m^{6}A modification regulates autophagy through post-transcriptional control of key mRNAs (e.g., ATG5 and Beclin1), thereby balancing tumor cell survival and death [12, 13]. It facilitates metabolic adaptation through glucose uptake enhancement [14] and lipid biosynthesis activation [15], while promoting immune escape via PD-L1/CTLA-4 checkpoint regulation [16]. Notably, aberrant m^{6}A landscapes contribute to resistance against chemotherapy, molecular targeted therapies, and immune checkpoint inhibitors [17, 18]. Although the role of m^{6}A in cancer has been extensively studied, its complex effects in regulating autophagy and apoptosis, as well as the tissue-specific regulatory networks in tumor cell

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metabolism and the microenvironment, have not been systematically elucidated. This has hindered the development of precision treatment strategies and clinical translation.

This review systematically examines the mechanistic roles of m^{6}A modifications in tumor autophagy and apoptosis, metabolism, and tumor microenvironment, focusing on context-specific regulatory networks across cancers (Figure 1). It further explores the prospect of drug development and targeting strategies based on m^{6}A regulatory molecules, and provides a new theoretical basis and research direction for tumor precision treatment.

Architectural framework of m^{6}A regulatory machinery

The discovery of fat mass and obesity-associated protein (FTO) as the first m^{6}A demethylase in 2011 revolutionized our understanding of RNA epigenetics by establishing m^{6}A as a reversible modification [19]. This breakthrough was followed by the identification of RRACH (R=G/A; H=A/C/U) as the consensus motif, predominantly localized in 3'UTRs and final exons of non-coding RNAs through high-throughput sequencing [2, 20]. The core regulatory mechanism of m^{6}A modification involves coordinated interactions among three functional protein groups: "Writers", "Erasers", and "Readers", which collectively mediate the dynamic deposition, removal, and interpretation of this RNA modification [21].

m^{6}A writers

The installation of m^{6}A modifications is catalyzed by a methyltransferase complex composed of Methyltransferase-like 3 (METTL3), Methyltransferase-like 14 (METTL14), and Wilms' tumor 1-associating protein (WTAP) [22]. METTL3 is the SAM-binding catalytic core for m^{6}A deposition, while METTL14 stabilizes the heterodimer through its RGG domain and enhances RNA binding, forming a composite active site that targets specific transcripts. On one hand, this complex can control the stability of target mRNAs through an m^{6}A-dependent mechanism, i.e., recognition by reader YTH domain-containing family protein [23]. Meanwhile, it can also promote oncogene expression through an m^{6}A-independent manner, in which cytoplasmic METTL3 directly recruits translation machinery (e.g., eukaryotic initiation factor 3, eIF3) [24]. The abnormal upregulation of METTL3/14 in cancer alters the m^{6}A landscape on key mRNAs (MYC, MYB, and PES1), thereby driving oncogene translation and leukemogenesis [25]. WTAP stabilizes this core complex and facilitates its localization to nuclear speckles [26]. Additionally, RNA-binding motif protein 15 (RBM15), Vir-like m^{6}A methyltransferase-associated protein (VIRMA), and Zinc finger CCCH-type containing 13 (ZC3H13) are recognized as components of the m^{6}A methyltransferase complex [27], though only METTL3 exhibits catalytic activity [28].

m^{6}A erasers

The RNA m^{6}A demethylases – fat mass and obesity-associated protein (FTO), ALKB homolog 5 (ALKBH5), and ALKB homolog 3 (ALKBH3) – belong to the ALKB dioxygenase family and require α-ketoglutarate and Fe^{2+} as cofactors to catalyze m^{6}A removal [29]. Structurally, these enzymes feature shallow substrate-binding clefts, restricting their activity primarily to single-stranded RNAs such as mRNA [30]. FTO dynamically regulates RNA metabolism (splicing, stabilization, and translation) mainly by demethylating the m^{6}A modification inside the mRNA and has secondary activity on the cap m^{6}Am under specific circumstances [31]. Current research confirms that ALKBH5 mediates m^{6}A demethylation in mRNAs and lncRNAs/non-coding RNAs [32, 33], while ALKBH3, the newest m^{6}A demethylase identified [34], is also involved in N1-methyladenine (m^{1}A) RNA modification pathways [35]. The dynamic reversibility of m^{6}A modifications is governed by the interplay between "writers" and "erasers", while their biological functions ultimately depend on recognition by "readers" [36].

m^{6}A readers

The YT521-B homology (YTH) domain-containing proteins represent a fundamental class of m^{6}A reader proteins that play pivotal roles in RNA metabolism regulation [37–39]. Among these, YTH domain-containing family protein 2 (YTHDF2) specifically recognizes m^{6}A-modified RNA through its characteristic C-terminal aromatic cage structure, composed of conserved residues including Trp432 and Trp486 [40]. This recognition enables YTHDF2 to facilitate RNA degradation through two distinct mechanisms: either by direct recruitment of the CCR4/NOT deadenylase complex via its N-terminal domain, or through the YTHDF2-HRSP12-RNase P/MRP pathway [41]. In contrast, YTHDF1 employs a similar aromatic cage structure (containing Trp411) for m^{6}A recognition but functions primarily in translation activation through its interaction with eukaryotic initiation factor 3 (eIF3) [42]. YTHDF3 cooperates with both YTHDF1 and YTHDF2 to regulate RNA translation or degradation [43, 44]. The activities of these YTH domain proteins are subject to sophisticated cellular regulation: YTHDF2 stability is enhanced through ERK1/2-mediated phosphorylation under hypoxic conditions, while its transcriptional expression is modulated by histone H3K18 lactylation [45]. Furthermore, competitive interactions between different m^{6}A readers, such as the competition between YTHDF proteins and Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) for m^{6}A binding sites on c-Myc mRNA, create an additional layer of regulatory complexity in determining RNA processing outcomes [46].

Other YTH family members include YTH domain-containing 1 (YTHDC1) and YTHDC2, which mediate RNA splicing or degradation through m^{6}A recognition [47]. Beyond YTH domain proteins, additional proteins serve as m^{6}A readers. For instance, IGF2BPs (IGF2BP1/2/3) recognize m^{6}A modifications primarily within the 3' UTRs of target mRNAs, where they recruit stabilizing factors and translation enhancers to suppress deadenylation and promote polysome assembly, thereby enhancing mRNA stability and translation efficiency [48]. Heterogeneous nuclear ribonucleoproteins (HNRNPs) such as HNRNPA2/B1 facilitate the processing of primary microRNA (pri-miRNA) transcripts by recognizing m^{6}A marks [49], while HNRNPC and HNRNPG regulate mRNA abundance and

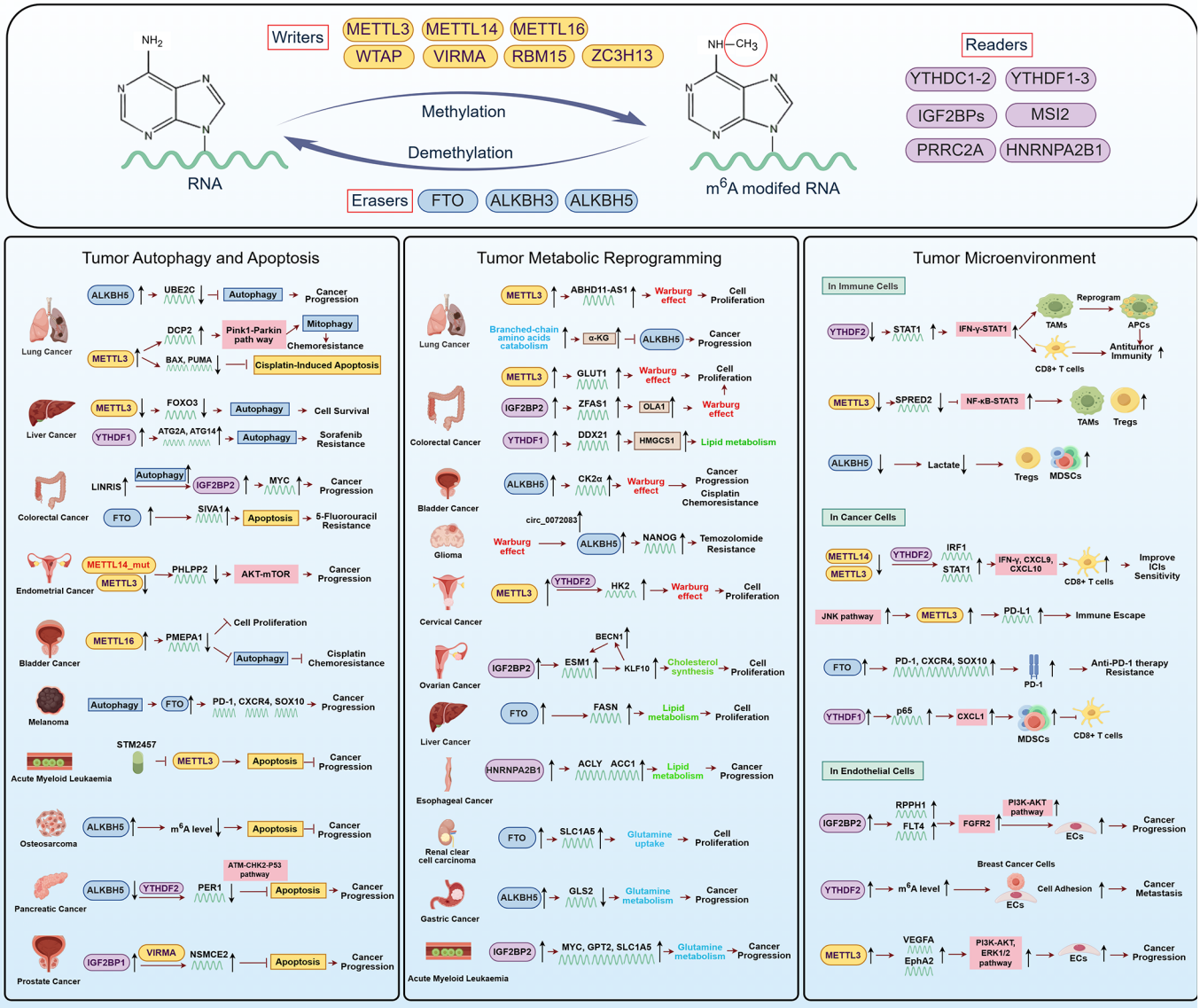

Figure 1. The main components of m^{6}A modification and the mechanism of the corresponding molecules in tumor autophagy and apoptosis, metabolic reprogramming and tumor microenvironment. This figure created by Figdraw (https://www.figdraw.com/).

splicing through m^{6}A-dependent mechanisms [50–52]. Nevertheless, the precise molecular mechanisms by which these factors coordinate m^{6}A-mediated regulation of cellular processes and disease pathogenesis remain to be fully elucidated.

The regulatory role of m^{6}A modifications in tumor autophagy and apoptosis

Tumor autophagy

Autophagy represents an evolutionarily conserved catabolic process essential for eukaryotic cellular homeostasis [53]. Dysregulated autophagy is closely associated with diverse physiological and pathological processes, including cellular homeostasis, aging, neurodegenerative disorders, and cancer [54]. Autophagy is broadly categorized into three types – macroautophagy, microautophagy, and chaperone-mediated autophagy – all operating through the autophagic-lysosomal pathway (ALP) [55, 56]. Among these, macroautophagy (hereafter referred to as autophagy) represents the predominant form [55]. Studies demonstrate that during early tumorigenesis, autophagy exerts tumor-suppressive effects through its dual functionality as a cell survival pathway and a quality control mechanism, effectively inhibiting tumor initiation and progression [57]. However, when tumors progress to advanced stages and establish under environmental stress, autophagy undergoes functional reprogramming into a dynamic degradation and recycling system. This transition not only sustains the survival and proliferation of primary tumors but also promotes aggressive cancer phenotypes by enhancing metastatic potential [57].

The autophagic process is primarily divided into four distinct phases: initiation, formation of the isolation membrane and autophagosome, autophagosome-lysosome fusion, and autophagic degradation [58], with each phase being regulated by epigenetic modifications [59]. Among these regulatory

mechanisms, m^6A modification plays a pivotal role in modulating tumor-associated autophagy [60]. The mechanistic target of rapamycin (mTOR), a key regulator of autophagy initiation, serves as a critical downstream effector of the Phosphatidylinositol 3-kinase (PI3K)/AKT (Protein Kinase B) signaling pathway [61]. In endometrial cancer, m^6A modification has been shown to regulate AKT kinase activity, suggesting its involvement in autophagy modulation through the AKT-mTOR signaling axis [62]. Subsequent studies have further established the role of m^6A in autophagy regulation across various malignancies.

For instance, in non-small cell lung cancer (NSCLC), upregulation of the m^6A demethylase ALKBH5 drives tumor progression by reducing m^6A levels on UBE2C mRNA, thereby disrupting the UBE2C-mediated autophagy suppression axis [63]. In small cell lung cancer, the m^6A methyltransferase METTL3 promotes chemoresistance by targeting DCP2 to regulate Pink1-Parkin pathway-mediated mitophagy and mitochondrial dysfunction [64]. A study about hepatocellular carcinoma (HCC) reveals that METTL3 modulates sorafenib resistance through m^6A-dependent regulation of autophagy transcription factor FOXO3 under hypoxic tumor microenvironments [65]. Hypoxia-inducible factor 1α (HIF-1α) further enhances hepatocellular carcinogenesis by inducing YTHDF1 expression, which drives autophagy and cancer progression via translational upregulation of ATG2A and ATG14 [66]. In bladder cancer, METTL16 binds to m^6A sites in the 3'-UTR of PMEPA1 mRNA, reducing its stability to suppress tumor proliferation while enhancing cisplatin sensitivity through PMEPA1-mediated autophagy pathways [67]. In colon cancer, autophagy caused by insufficient cell energy promotes the expression of m^6A reading protein IGF2BP2, stabilizes MYC mRNA, and then promotes the glycolysis process of tumor cells, thereby increasing cell energy supply and promoting the proliferation of cancer cells [68]. Melanoma studies highlight the critical role of the m^6A demethylase FTO in therapeutic resistance, where nutrient-deprived tumor microenvironments induce autophagy-mediated FTO upregulation. This reduces m^6A levels on PD-1, CXCR4, and SOX10 mRNAs, attenuating YTHDF2-mediated degradation and potentiating immune evasion [69].

In summary, accumulating evidence demonstrates that m^6A RNA methylation participates in dysregulated autophagy signaling and plays a critical role in the pathogenesis and progression of diverse malignancies. Therefore, comprehensive elucidation of the regulatory interplay between m^6A modifications and autophagy-related molecules, as well as their functional implications in cancer advancement and therapeutic responses, will not only advance our understanding of novel oncogenic mechanisms but also provide a critical theoretical framework for developing targeted therapeutic strategies centered on the m^6A-autophagy regulatory axis.

Tumor apoptosis

Apoptosis, a canonical form of programmed cell death, plays a fundamental role in maintaining tissue homeostasis by eliminating harmful cells with DNA damage or aberrant proliferation [70]. In recent years, the critical involvement of apoptotic regulation in tumorigenesis and cancer progression has garnered substantial research attention. Emerging evidence indicates that neoplastic cells acquire apoptosis resistance mechanisms to evade immune surveillance and programmed cell death, conferring not only significant survival advantages but also promoting malignant transformation and disease progression. Notably, such apoptotic resistance represents a pivotal factor contributing to the failure of conventional chemotherapy and targeted therapies, posing a major scientific challenge in current oncology therapeutics [71].

Recent studies have revealed the crucial regulatory role of m^6A modification in tumor cell apoptosis, though mechanistic investigations remain relatively limited. The m^6A "writers", "erasers", and "readers" orchestrate apoptosis through context-dependent mechanisms across cancers.

The m^6A methyltransferase METTL3 has been demonstrated to be intimately associated with the initiation and maintenance of acute myeloid leukemia (AML). Strikingly, its specific inhibitor STM2457 markedly suppresses leukemic cell proliferation while inducing apoptosis and differentiation [72]. Similarly, loss of METTL3 in NSCLC enhances cisplatin-induced apoptosis by upregulating BAX and PUMA gene via reduced m^6A methylation on their transcripts [73]. A recent study shows that the stapled peptide inhibitor RSM3 targeting METTL3-METTL14 binding inhibits complex formation, promotes METTL3 proteasomal degradation, reduces global RNA methylation, upregulates apoptosis-related genes, suppresses pro-cancer signals, and inhibits tumor growth with enhanced apoptosis in vivo, offering a novel mechanism distinct from small-molecule inhibitors for METTL3-targeted cancer therapy [74].

Among m^6A demethylases, decreased ALKBH5 expression correlates with poor prognosis in osteosarcoma patients. Functional studies show that ALKBH5 upregulation reduces m^6A levels in osteosarcoma cells, consequently inhibiting proliferation and promoting apoptosis alongside cell cycle arrest [75]. In pancreatic cancer, ALKBH5 loss drives cancer progression via YTHDF2-dependent PER1 m^6A demethylation, inhibiting apoptosis through the ATM-CHK2-P53 pathway [76]. Conversely, FTO mediates fluorouracil (5-FU) resistance in colorectal cancer through m^6A-dependent regulation of the apoptotic gene SIVA1 [77]. Notably, in prostate cancer, IGF2BP1 stabilizes NSMCE2 mRNA in an m^6A-dependent manner by recognizing VIRMA-mediated methylation, thereby reducing reactive oxygen species (ROS) levels and apoptosis to promote tumor progression [78].

In all, the dynamic interplay between m^6A RNA methylation, autophagy, and apoptosis highlights its critical role in tumor biology as a key link for cancer progression and treatment resistance. Emerging evidence highlights that m^6A-modifying enzymes orchestrate context-dependent regulatory networks that influence autophagy and apoptosis, with important effects on tumor survival, metastasis, and drug sensitivity. However, substantial challenges persist, encompassing the dual roles of m^6A regulators in mediating autophagy-apoptosis crosstalk and the tissue-specific heterogeneity of their functional outcomes. Future investigative priorities should focus on deciphering the spatiotemporal kinetics of m^6A regulation, its synergistic or antagonistic interactions with other epigenetic

modalities, and the rational design of therapeutic interventions tailored to specific tumor microenvironments. Targeting the m^{6}A-autophagy-apoptosis axis holds significant translational potential for overcoming therapeutic resistance, yet its clinical realization hinges on resolving the paradoxical functions of these enzymes in malignant transformation and microenvironmental modulation.

The role of m^{6}A modification in tumor metabolic reprogramming

Early studies have established cancer as a genetic disease, with nearly all cancers driven by genetic alterations. Substantial evidence indicates that all cancer cells exhibit six core biological capabilities: sustaining proliferative signaling, evading growth suppressors, resisting cell death and apoptosis, achieving limitless replicative potential, inducing angiogenesis, and promoting invasion and metastasis [79]. Subsequent research has identified two additional canonical traits-metabolic reprogramming and immune evasion [71]. The latest advances further expand this conceptual framework by introducing new hallmarks and enabling characteristics, including phenotypic plasticity, nonmutational epigenetic reprogramming, polymorphic microbiomes, and the functional role of senescent cells in the tumor microenvironment [80]. Accumulating evidence indicates that m^{6}A modifications participate in modulating key metabolic pathways in malignancies, including glucose, fatty acid, and amino acid metabolism. Consequently, cancer can no longer be viewed solely through a genetic lens but must also be understood as a metabolic disease. Exploring the mechanism of metabolic reprogramming of cancer is helpful for a better understanding of the oncogenesis and progression process, thereby facilitating the identification of effective therapeutic targets for cancer.

Glucose metabolism

As the most extensively studied facet of tumor metabolic reprogramming, glucose metabolism exemplifies how m^{6}A modification reshapes cancer cell bioenergetics. Dysregulated glucose metabolism, a hallmark of tumor metabolic reprogramming, manifests as enhanced glycolytic flux and lactate fermentation (the Warburg effect). This metabolic adaptation empowers cancer cells to mitigate metabolic stress, thrive in hostile microenvironments, and sustain malignant proliferation [81]. Mechanistically, m^{6}A regulators orchestrate glucose metabolism through both upstream signaling and direct modulation of glycolytic effectors. Investigations in temozolomide-resistant gliomas reveal that the Warburg effect promotes extracellular vesicle-mediated release of circ-0072083, which targets the miR-1252-5p/ALKBH5 axis to reduce m^{6}A modification on NANOG mRNA, a core pluripotency transcription factor, thereby stabilizing its expression and exacerbating chemoresistance [82]. In colorectal cancer, overexpression of the m^{6}A reader IGF2BP2 stabilizes the ZFAS1/OLA1 axis, augmenting obg-like ATPase 1 (OLA1) recruitment, ATP hydrolysis, and glycolytic activity to activate the Warburg effect, ultimately enhancing tumor cell proliferation and clonogenicity [83]. Furthermore, in NSCLC, METTL3-mediated m^{6}A methylation of the long non-coding RNA ABHD11-AS1 enhances its stability and expression, consequently stimulating Warburg metabolism and malignant cell growth [84].

At the effector level, m^{6}A directly fine-tunes rate-limiting enzymes and transporters to drive glycolytic dependency. For instance, METTL3-mediated m^{6}A modification at the 3'UTR of hexokinase 2 (HK2) mRNA, the rate-limiting enzyme in glycolysis, cooperates with YTHDF1 to stabilize its transcript, thereby potentiating the Warburg effect in cervical carcinogenesis [85]. METTL3 further orchestrates m^{6}A-dependent regulation of the glucose transporter isoform 1 (SLC2A1; GLUT1), relying on IGF2BP2/3 to stabilize its expression and activate downstream glycolytic pathways, ultimately driving colorectal cancer progression [86]. In bladder cancer, ALKBH5 downregulation modulates m^{6}A-dependent stability of casein kinase 2 alpha subunit (CK2α) mRNA, suppressing CK2α-mediated glucose uptake, lactate/ATP production, and tumorigenesis while enhancing cisplatin sensitivity [87]. Additionally, key metabolic regulators, including pyruvate kinase M2 (PKM2), cellular myelocytomatosis oncogene (C-Myc), and non-canonical glycolytic enzymes like pyruvate dehydrogenase kinase 1 (PDK1), are subject to m^{6}A-mediated regulation, collectively shaping tumor progression trajectories [88–90].

Lipid metabolism

Within the tumor microenvironment, nutrient deprivation drives cancer cells to reprogram lipid metabolism to sustain proliferation, survival, invasion, and metastatic capabilities [91]. Beyond glucose metabolism, m^{6}A modification emerges as a key orchestrator of lipid metabolic reprogramming, enabling cancer cells to survive nutrient-deprived microenvironments. Studies demonstrate that FTO knockout significantly reduces de novo lipogenesis enzyme levels and lipid content in HCC cells. Mechanistically, FTO ablation elevates m^{6}A modification on fatty acid synthase (FASN) mRNA, which is recognized by YTHDF2 to destabilize the transcript, thereby reducing protein levels of acetyl-CoA carboxylase (ACC) and ATP-citrate lyase (ACLY). This lipid biosynthesis impairment ultimately induces HCC cell death due to insufficient lipid accumulation [92].

In colorectal cancer, YTHDF1 enhances the mRNA stability of DDX21 by recognizing its m^{6}A modification site, which further binds to the promoter region of 3-hydroxy-3-methylglutaryl-coa synthase 1 (HMGCS1) and directly activates HMGCS1 transcription to promote tumor progression [93]. Furthermore, in esophageal squamous cell carcinoma (ESCC), the m^{6}A reader HNRNPA2B1 upregulates fatty acid metabolism-related genes ACLY and ACC1, facilitating lipid droplet formation and promoting tumor cell proliferation, migration, and invasion [94]. In ovarian cancer, the m^{6}A reading protein IGF2BP3 promotes cholesterol synthesis and inhibits lipolysis by regulating the ESM1/KLF10/BECN1 feedback loop, thereby promoting tumor progression [95]. These findings collectively illustrate how m^{6}A readers establish a pro-lipogenic state to support tumor cell bioenergetics and membrane synthesis.

Amino acid metabolism

The m^6A modification also intersects with amino acid metabolism, linking nutrient availability to epigenetic reprogramming and metastatic potential. In clear cell renal cell carcinoma, the m^6A RNA demethylase FTO forms a synthetic lethal partnership with VHL through m^6A modification-dependent regulation of the glutamine transporter SLC1A5. FTO-mediated demethylation of SLC1A5 mRNA enhances its stability and expression, thereby promoting glutamine uptake and metabolic reprogramming in VHL-deficient cells [96]. Similarly, ALKBH1 functions as an m^6A demethylase, catalyzing demethylation at critical residues (Y184, H231, D233) to enhance lung cancer cell migration and invasion [97]. Notably, this regulatory axis extends to branched-chain amino acid metabolism.

Branched-chain amino acids catabolism depletes α-KG levels, suppressing ALKBH5 demethylase function and consequently elevating m^6A methylation on EMT-related transcripts, ultimately promoting NSCLC brain metastasis through this epigenetic pathway [98]. Similarly, the curcumin analog WZ35 disrupts glutamine metabolism by targeting the GLS2-ALKBH5-m^6A regulatory axis, leading to glutathione depletion and consequent suppression of gastric cancer metastasis [99]. In AML, the m^6A reader protein IGF2BP2 sustains leukemia stem cells through m^6A-dependent regulation of glutamine metabolism genes (MYC, GPT2, SLC1A5). Pharmacological targeting of IGF2BP2 with CWI1-2 disrupts this metabolic axis, thereby offering a promising therapeutic strategy for AML [100]. These studies reveal a bidirectional relationship between amino acid availability, m^6A dynamics, and tumor cell plasticity.

The role of m^6A modification in the tumor microenvironment

Immunosuppression constitutes a central hallmark of the tumor microenvironment (TME), primarily characterized by functional exhaustion of cytotoxic immune cells, dysfunction of antigen-presenting cells (APCs), and extensive recruitment or induction of immunosuppressive cell populations. These inhibitory immune components include $CD4^+$ regulatory T cells (Tregs), immature myeloid cells (iMCs)/myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and various immunosuppressive cytokines [101, 102]. In addition, endothelial cells in the tumor microenvironment mediate tumor immunosuppression by expressing immunosuppressive molecules [103], inhibiting leukocyte adhesion/activation, and recruiting immunosuppressive cells [104], which ultimately promote immune escape and tumor progression [105]. During tumor progression, infiltrating immune cells undergo remodeling processes that profoundly impact their intrinsic biological functions. These alterations can facilitate immune evasion while sustaining the proliferative capacity of tumor cells [102]. Emerging evidence suggests that m^6A modification may be implicated in tumor immune remodeling processes through multifaceted regulatory mechanisms.

Regulation of immune cell function

The m^6A machinery differentially modulates immune cell activity through distinct molecular pathways. For instance, YTHDF2 binds m6A-modified STAT1 mRNA in TAMs, promoting its decay. Inhibition of YTHDF2 activates IFNγ-STAT1 signaling to reprogram TAMs, thereby enhancing $CD8^+$ T cell-mediated antitumor immunity and offering a potential strategy to improve immune checkpoint therapy efficacy [106]. METTL3-mediated m^6A modification enables YTHDF1 to promote SPRED2 translation, suppressing NF-κB/STAT3 pathways in TAMs [107]. Furthermore, YTHDF1 modulates dendritic cells (DCs) by regulating the translation of lysosomal proteases via m6A modification, impairing tumor antigen cross-presentation and $CD8^+$ T cell cross-priming, thereby limiting antitumor immunity [108].

Tumor-intrinsic immune modulation

In addition to immune cells, intrinsic m^6A modifications in tumor cells profoundly influence immune remodeling processes in the TME. Studies reveal that inhibition of m^6A methyltransferases METTL3 and METTL4 stabilizes STAT1 and IRF1 mRNAs through a YTHDF2-dependent mechanism, activating the IFN-γ-STAT1-IRF1 signaling axis. This activation enhances $CD8^+$ T cell infiltration and cytokine secretion, thereby potentiating the efficacy of PD-1 blockade therapy [109]. In melanoma, FTO-mediated m^6A demethylation contributes to immunotherapy resistance by upregulating key genes, including PD-1, CXCR4, and SOX10. Conversely, pharmacological inhibition of FTO enhances tumor responsiveness to IFN-γ and overcomes PD-1 inhibitor resistance [69]. Furthermore, YTHDF1 facilitates melanoma immune evasion and resistance to immune checkpoint inhibitors by promoting degradation of major histocompatibility complex class I (MHC-I) molecules [110].

In colon cancer, YTHDF1 enhances p65 translation via m^6A modification, subsequently elevating CXCL1 expression. This upregulation recruits MDSCs through the CXCL1-CXCR2 axis, thereby accelerating tumor progression and immunotherapy resistance [17]. Breast cancer studies demonstrate that the METTL3/IGF2BP3 axis upregulates PD-L1 expression via m^6A modification, enabling cancer cell immune evasion [111]. In bladder cancer, JNK signaling activates c-Jun to promote METTL3 expression, which stabilizes PD-L1 mRNA through m^6A modification, amplifying PD-L1 expression and fostering immune escape. Inhibition of the JNK/METTL3 axis reduces PD-L1 levels and enhances $CD8^+$ T cell-mediated antitumor activity [112]. Additionally, loss or inhibition of the m^6A demethylase ALKBH5 enhances tumor sensitivity to immune checkpoint blockade (ICB) therapy by remodeling lactate metabolism and reshaping immunosuppressive cellular components within the TME, thereby potentiating immunotherapeutic outcomes [113]. Targeting the demethylase FTO has also been found to suppress cancer stem cell properties and immune evasion mechanisms [114]. These findings collectively unveil a multidimensional regulatory network of m^6A modifications in tumor cell-TME interactions.

Vascular remodeling

Accumulating evidence highlights the pivotal role of m^{6}A RNA modification in modulating endothelial cell plasticity and tumor vascularization. In hypoxic breast cancer microenvironments, RPPH1 upregulation stabilizes FGFR2 mRNA via the IGF2BP2-m^{6}A axis, activating PI3K/AKT signaling to enhance EC-driven angiogenesis, cancer stemness, and metastasis [115]. Similarly, IGF2BP2 interacts with FLT4 in lung adenocarcinoma, amplifying PI3K/AKT phosphorylation to promote EC proliferation and vascular lumen formation [116]. Beyond mRNA stabilization, the m^{6}A reader YTHDF3 facilitates breast cancer brain metastasis by enhancing the translation of m^{6}A-enriched transcripts (e.g., ST6GALNAC5, GJA1, and EGFR), thereby strengthening tumor cell adhesion to brain ECs and promoting transendothelial invasion [117]. Additionally, METTL3-mediated m^{6}A deposition coordinates IGF2BP2/3-dependent stabilization of EphA2 and VEGFA in colorectal cancer, activating PI3K/AKT/mTOR and ERK1/2 pathways to drive vasculogenic mimicry (VM), a process enabling tumor cells to adopt EC-like phenotypes and form perfusion-supporting channels [118]. Collectively, these findings highlight m^{6}A machinery as a multifaceted regulator of EC-tumor crosstalk, driving angiogenesis, metastatic niche formation, and therapy-resistant vascular remodeling, thus presenting novel targets for anti-cancer strategies.

Conclusion and future perspectives

In recent years, m^{6}A modification, as a central research focus in epitranscriptomics, has increasingly been recognized for its regulatory roles in tumorigenesis. This review systematically delineates the dynamic regulatory mechanisms of m^{6}A modification and its multifaceted roles in tumor progression. First, it outlines the molecular basis of m^{6}A modification, which involves three core enzyme classes, writers (METTL3/14/16, WTAP, VRIMA, RBM15, ZC3H13), erasers (FTO, ALKBH3/5), and readers (YTHDFs, YTHDCs, IGF2BPs, HNRNPA2B1, MSI2), that dynamically regulate RNA stability, translation efficiency, and subcellular localization, thereby influencing tumor cell proliferation, metastasis, and drug resistance. Subsequently, this review comprehensively discusses the regulatory roles of m^{6}A modification in tumor autophagy and apoptosis, metabolic reprogramming, and tumor microenvironment dynamics.

This review reveals that m^{6}A-modifying enzymes (writers, erasers, and readers) exhibit paradoxical tumor-regulatory roles across cancer types and microenvironments. For example, METTL3 promotes sorafenib resistance via FOXO3-mediated autophagy in hypoxic HCC [65], but enhances cisplatin sensitivity by upregulating BAX/PUMA in NSCLC [73]. ALKBH5 drives NSCLC progression by activating UBE2C-mediated autophagy [63], yet suppresses osteosarcoma growth via global m6A reduction [75]. FTO enables melanoma immune evasion by stabilizing PD-1/CXCR4 mRNAs [69], while inducing HCC cell death via FASN-dependent lipid biosynthesis impairment [92]. These contradictions highlight context-dependent targeting of survival/apoptotic, metabolic/immune pathways, underscoring the complexity of epitranscriptomic regulation in cancer.

Although significant progress has been made in understanding m^{6}A modifications in oncology, several critical gaps and challenges remain. Firstly, emerging evidence suggests that m^{6}A-modifying enzymes themselves are epigenetically regulated, which is a complex interaction that requires systematic study. Moreover, the substantial heterogeneity among tumors necessitates further elucidation of tumor-type-specific m^{6}A regulatory mechanisms. Additionally, recent studies have uncovered non-canonical m^{6}A regulators, such as non-canonical cap-binding protein eIF3d, mediating stress response via ALKBH5-dependent demethylation [119], IGF2BP1 recognizing m^{6}A through a hydrophobic platform independent of YTH proteins [120], METTL14 binding to RNA G-quadruplexes to guide methylation [121], and the RNA helicase DDX21 directs co-transcriptional m^{6}A deposition by interacting with METTL3 to recognize R-loops and promote RNAPII termination [122], highlighting emerging regulatory mechanisms beyond canonical writer/reader/eraser pathways.

From a translational standpoint, four strategic priorities emerge: (1) Systematic identification of m^{6}A regulators and their downstream targets as dual-function biomarkers for both prognostic evaluation and immunotherapy response prediction; (2) Development of precision therapeutics combining m^{6}A-targeted small-molecule modulators with immune checkpoint blockade therapies to achieve synergistic antitumor efficacy; (3) Establishment of dynamic m^{6}A regulatory network models through artificial intelligence-powered multi-omics integration, enabling comprehensive analysis of tumor progression mechanisms; (4) Implementing clinically representative model systems, particularly patient-derived xenograft (PDX) models and patient-derived organoid (PDO) models, combined with multi-omics validation using clinical specimens. This integrated approach will facilitate the translation of fundamental discoveries into clinical applications, ultimately advancing precision therapeutic strategies for cancer patients.

In conclusion, as a critical bridge linking the epitranscriptome with functional tumor phenotypes, m^{6}A modification research has not only deepened our understanding of malignant biological behaviors in oncology but also established theoretical frameworks for developing novel diagnostic tools and combination therapeutic strategies. Future investigations should prioritize two synergistic dimensions: mechanistic depth and clinical translation.

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Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

This review has no associated data generated.

Author contribution statement

Conceptualization, S.X., Y.L.; Writing-original draft, Y.L., K.Z.; Writing-reviewing, Y.F., S.Y., Y.H., X.X., Z.H.; Writing-reviewing and editing, Y.L., K.Z., S.X.

Ethics approval

Ethical approval was not required.

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