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REVIEW

Roles and implications of mRNA N^6-methyladenosine in cancer

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Abstract

RNA N^6-methyladenosine modification is the most prevalent internal modification of eukaryotic RNAs and has emerged as a novel field of RNA epigenetics, garnering increased attention. To date, m^6A modification has been shown to impact multiple RNA metabolic processes and play a vital role in numerous biological processes. Recent evidence suggests that aberrant m^6A modification is a hallmark of cancer, and it plays a critical role in cancer development and progression through multiple mechanisms. Here, we review the biological functions of mRNA m^6A modification in various types of cancers, with a particular focus on metabolic reprogramming, programmed cell death and tumor metastasis. Furthermore, we discuss the potential of targeting m^6A modification or its regulatory proteins as a novel approach of cancer therapy and the progress of research on m^6A modification in tumor immunity and immunotherapy. Finally, we summarize the development of different m^6A detection methods and their advantages and disadvantages.

KEYWORDS
cancer therapy, immunotherapy, m^6A methylation, N^6-methyladenosine

Abbreviations: 2OG, 2-oxoglutarate; 4SU, 4-thiouridine; ACC1, Acetyl-CoA carboxylase 1; ACLY, ATP citrate lyase; ACSL, Acyl-CoA synthetase; AKR1C1, Aldo-keto reductase family 1 member C1; AKT, Protein kinase B; ALKBH5, alkB homolog 5; AML, acute myeloid leukemia; APOBEC1, apolipoprotein B mRNA editing catalytic subunit 1; ATAR, All-trans retinoic acid; ATF4, Activating Transcription Factor 4; ATG2A, Autophagy Related 2A; BATF2, Basic Leucine Zipper ATF-Like Transcription Factor 2; BC, breast cancer; BCL-2, B-cell lymphoma 2; BHLHE41, Basic helix-loop-helix family member e41; C/EBPβ, CCAAT/enhancer-binding protein beta; carRNAs, chromosome-associated regulatory RNAs; CC, cervical cancer; Cish, Cytokine-Inducible SH2-Containing Protein; CoREST, Co-repressor for element-1-silencing transcription factor; CRC, colorectal cancer; CtBP, C-terminal binding protein; CXCL1, C-X-C Motif Chemokine Ligand 1; CXCR4, C-X-C Chemokine Receptor Type 4; DART-seq, deamination adjacent to RNA modification targets; DCs, dendritic cells; DDIT4, DNA damage-inducible transcript 4; DGCR8, DiGeorge syndrome critical region 8; E2F, E2 promoter binding factor; EGFR, Epidermal Growth Factor Receptor; eIF3, eukaryotic translation initiation factor 3; eIF4G1, Eukaryotic Initiation Factor 4 Gamma 1; EMT, epithelial-mesenchymal transition; ENO2, Enolase 2; ERK, Extracellular Signal-Regulated Kinase; ESCC, esophageal squamous cell carcinoma; FBXW7, F-box and WD repeat domain-containing 7; FGFR4, Fibroblast Growth Factor

1 | INTRODUCTION

RNA modifications are highly conserved and common in most eukaryotic species. With the improved methodologies, our understanding of RNA modifications has become more extensive and advanced. To date, more than 160 different types of RNA chemical modifications have been identified [1, 2]. Among them, RNA N^6-methyladenosine (m^6A) is the most abundant and best-characterized modification in coding and non-coding RNAs. Specifically, m^6A modification mainly occurs in the RRACH (R denotes A or G; H denotes A, C, or U) motif, and its abundance is highest at the 3' untranslated regions (UTRs), stop codons and within long internal exons [3–6].

As a dynamic and reversible RNA modification, m^6A modification is mainly regulated by the coordinated actions of the following three different classes of proteins: enzymes that catalyze the methylation of RNA are commonly referred to as "writers" (m^6A methyltransferases), enzymes that remove methyl groups from RNA are called "erasers" (m^6A demethylases), and "readers" (m^6A-specific binding proteins) are a class of proteins that specifically recognize m^6A modification [7–12].

More recently, the functional importance of m^6A modification has been reported in various RNA metabolism processes, including pre-mRNA splicing [13], nuclear export [14], translation regulation [15], mRNA decay [16], non-coding RNA processing [17] and RNA structural remodeling [18]. Moreover, m^6A modification can affect a variety of cellular and physiological processes and plays a vital role in circadian rhythm control [19], stem cell self-renewal and differentiation [20, 21], heat shock response [22], DNA damage response [23], spermatogenesis [24, 25] and maternal-to-zygotic transition [26]. The study of m^6A in the field of cancer began in 2017. Li et al. [27] demonstrated that the fat mass and obesity-associated protein (FTO) plays an oncogene role in acute myeloid leukemia. Zhang et al. [28] revealed that alkB homolog 5 (ALKBH5) plays an essential role in maintaining cell stemness in malignant glioma cells. Furthermore, numerous studies have shown that m^6A modification and its regulatory proteins have a significant impact on tumorigenesis and progression [29–32].

In this review, we aim to explore the biological functions of m^6A modification in the development and progression

Receptor 4; FOXM1, Forkhead Box M1; FPN1, Ferroportin 1; FTO, fat mass and obesity-associated protein; FXR1, Fragile X Mental Retardation Autosomal Homolog 1; GC, gastric cancer; GJA1, Gap Junction Alpha-1 Protein; GLORI, glyoxal and nitrite-mediated deamination of unmethylated adenosines; GLUT1, glucose transporter type 1; GSC, glioblastoma stem cell; HB, hepatoblastoma;; HCC, hepatocellular carcinoma; HDGF, Hepatoma-derived growth factor; HER2, Human Epidermal Growth Factor Receptor 2; HIF-1α, Hypoxia-Inducible Factor 1 alpha; HIVEP2, Human Immunodeficiency Virus type I Enhancer Binding Protein 2; HK2, Hexokinase 2; hnRNPA2B1, heterogeneous nuclear ribonucleoproteins A2/B1; hnRNPC, heterogeneous nuclear ribonucleoprotein C; hnRNPG, heterogeneous nuclear ribonucleoprotein G; HNRNPs, heterogeneous nuclear ribonucleoproteins; HOXA10, Homeobox A10; HuR, Human antigen R; ICB, immune checkpoint blockade; IDH1/2, isocitrate dehydrogenase 1/2; IFN-γ, Interferon-gamma; IGF1R, Insulin-like growth factor 1 receptor; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; IL-15, interleukin-15; IRF1, Interferon Regulatory Factor 1; JAK2, Janus Kinase 2; KDM3B, Lysine Demethylase 3B; KEAP1, Kelch-like ECH-associated protein 1; LATS2, Large tumor suppressor kinase 2; LDHA, Lactate dehydrogenase A; lncRNA, long non-coding RNA; LSD1, Lysine-specific demethylase 1; LUAD, lung adenocarcinoma; LXRA, Liver X Receptor alpha; m^1A, N^1-methyladenosine; m^6A-LAIC-seq, m^6A-Level and Isoform Characterization sequencing; m^6A-REF-seq, m^6A-sensitive RNA-endoribonuclease-facilitated sequencing; m^6A-SAC-seq, m^6A-selective allyl chemical labeling and sequencing; m^6A-SEAL, FTO-assisted m^6A selective chemical labeling method; m^6A-seq, N^6-methyladenosine–sequencing; m^6A, N^6-methyladenosine; m^6A_m, 2-O-dimethyladenosine; MA, meclofenamic acid; MALAT1, Metastasis-Associated Lung Adenocarcinoma Transcript 1; MAPK, Mitogen-Activated Protein Kinase; Mct4, Monocarboxylate transporter 4; MDSC, myeloid-derived suppressor cell; MeRIP-seq, methylated RNA immunoprecipitation and sequencing; METTL14, methyltransferase-like 14; METTL16, methyltransferase-like 16; METTL3, methyltransferase-like 3; METTL5, methyltransferase-like 5; miCLIP, m^6A individual-nucleotide resolution cross-linking and immunoprecipitation; mTOR, mammalian target of rapamycin; mTORC1, mechanistic Target of Rapamycin Complex 1; NANOG, Nanog homeobox protein; NAOX, nucleic acid oxygenase; NDUFA4, NADH:Ubiquinone Oxidoreductase Subunit A4; NF-κB, Nuclear Factor kappa B; NK, Natural killer; NRF2, Nuclear factor erythroid 2-related factor 2; NSCLC, non-small cell lung cancer; OLA1, Obg-like ATPase 1; OSCC, oral squamous cell carcinoma; PA-m^6A-seq, photo-crosslinking-assisted m^6A sequencing; PD-1, programmed cell death protein 1; PD-L1, Programmed Death Ligand 1; PKM2, Pyruvate kinase M2; PPAR-γ, Peroxisome Proliferator-Activated Receptor Gamma; PTC, papillary thyroid carcinoma; PTEN, Phosphatase and tensin homolog; R-2HG, R-2-hydroxyglutarate; RBM15, RNA Binding Motif Protein 15; RCC2, Regulator of Chromosome Condensation 2; RUNX1, Runt-related transcription factor 1; S6, Ribosomal protein S6; SHP-2, Src homology 2 domain-containing protein tyrosine phosphatase-2; SMAD3, SMAD family member 3; Snai2, Snail family zinc finger 2; SOCS1, Suppressor of Cytokine Signaling 1; SOX4, SRY-Box Transcription Factor 4; SPRED2, Sprouty-Related EVH1 Domain-Containing Protein 2; ST6GALNAC5, ST6 N-Acetylgalactosaminide Alpha-2,6-Sialyltransferase 5; STAT5, signal transducer and activator of transcription 5; TAMs, Tumor-associated macrophages; Tardbp, transactive response DNA binding protein; TCF4, Transcription Factor 4; TET1, Ten-Eleven Translocation 1; TLR4, Toll-Like Receptor 4; TNBC, triple negative breast cancer; TSC1, Tuberous Sclerosis Complex 1; TSCC, tongue squamous cell carcinoma; UTRs, untranslated regions; VASH1, Vasohibin-1; VEGFA, Vascular Endothelial Growth Factor A; VIRMA, Vir like m^6A methyltransferase associated; WTAP, Willms tumor 1 associated protein; YTH, YT521-B homology; YTH, YT521-B homology; YTHDC1, YTH domain-containing protein 1; YTHDC2, YTH domain-containing protein 2; YTHDFs, YTH domain-containing family proteins; ZC3H13, Zinc Finger CCCH-Type Containing 13; ZCCHC4, Zinc finger CCHC domain-containing protein 4; ZFAS1, Zinc Finger Antisense 1.

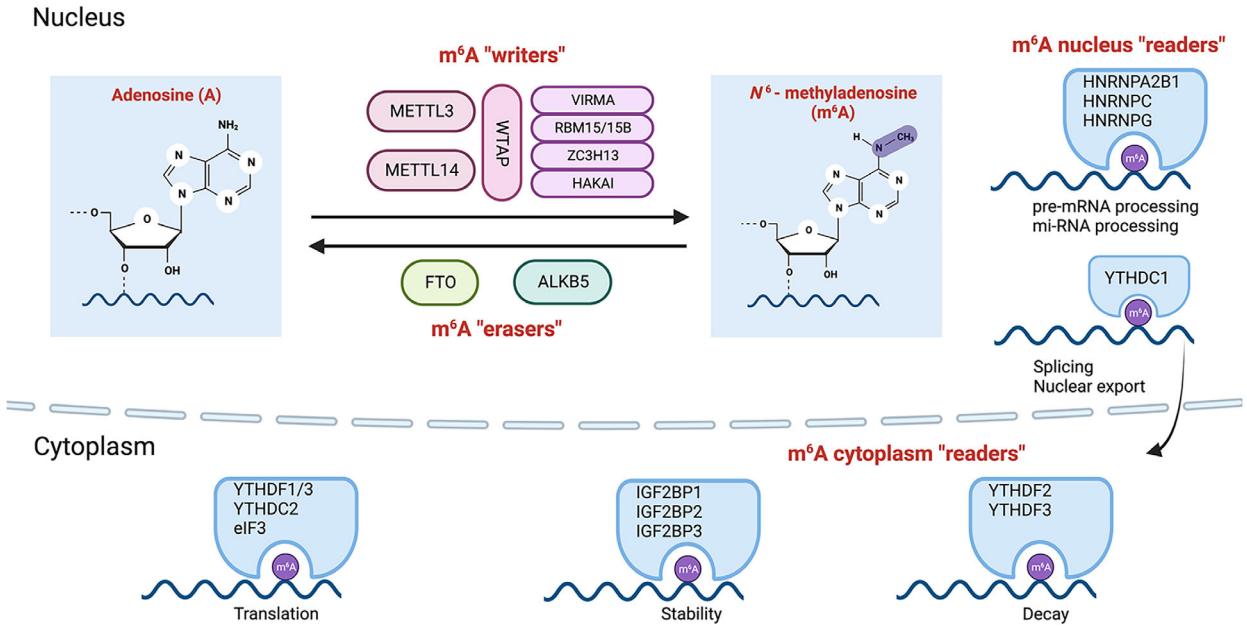

FIGURE 1 Regulators of m^{6}A methylation. There are three different classes of proteins: enzymes that catalyze the methylation of RNA are commonly referred to as "writers" (m^{6}A methyltransferases); enzymes that remove methyl groups from RNA are called "erasers" (m^{6}A demethylases); and "readers" (m^{6}A-specific binding proteins) are a class of proteins that specifically recognize m^{6}A modification. Abbreviations: ALKBH5, alkB homolog 5; eIF3, eukaryotic translation initiation factor 3; FTO, fat mass and obesity-associated protein; hnRNPA2B1, heterogeneous nuclear ribonucleoproteins A2/B1; hnRNPC, heterogeneous nuclear ribonucleoprotein C; hnRNPG, heterogeneous nuclear ribonucleoprotein G; HNRNPs, heterogeneous nuclear ribonucleoproteins; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; m^{6}A, *N*^{6}-methyladenosine; METTL14, methyltransferase-like 14; METTL16, methyltransferase-like 16; METTL3, methyltransferase-like 3; METTL5, methyltransferase-like 5; RBM15, RNA Binding Motif Protein 15; VIRMA, Vir like m^{6}A methyltransferase associated; WTAP, Willms tumor 1 associated protein; YTH, YT521-B homology; YTHDC1, YTH domain-containing protein 1; YTHDC2, YTH domain-containing protein 2; YTHDFs, YTH domain-containing family proteins; ZC3H13, Zinc Finger CCCH-Type Containing 13; ZCCHC4, Zinc finger CCHC domain-containing protein 4.

of various cancers. Specifically, we will examine its roles in metabolic reprogramming, programmed cell death, and tumor metastasis. We also discuss the molecular mechanisms underlying the m^{6}A in regulating therapeutic resistance and the potential of m^{6}A and its regulators as therapeutic targets. Additionally, we delve into the current research progress on m^{6}A modification and its roles in tumor immunity and immunotherapy. Furthermore, we summarize the various techniques used to detect m^{6}A modification, including their respective advantages and disadvantages. By highlighting the impact of m^{6}A modification and its regulatory pathways on cancer pathogenesis, we hope to provide insights into the development of more effective and targeted cancer treatments.

2 | REGULATORS OF m^{6}A METHYLATION

2.1 | m^{6}A writers

m^{6}A modification of mRNA is catalyzed by a multicomponent writer complex in a highly specific manner (Figure 1), including methyltransferase-like 3 (METTL3), METTL14, Willms tumor 1 associated protein (WTAP), RNA-binding motif protein 15 (RBM15) and its paralogue RBM15B, Vir like m^{6}A methyltransferase associated (VIRMA), zinc finger CCCH domain-containing protein 13 (ZC3H13), METTL16, zinc finger CCHC domain-containing protein 4 (ZCCHC4) and METTL5 [33–35]. Mechanistically, METTL3 and METTL14 form a stable heterodimeric core complex. METTL3 is the catalytically active subunit, while METTL14 plays a structural role critical for binding the target RNA [8, 36, 37]. WTAP is critical for the recruitment of the m^{6}A methyltransferase complex to mRNA targets and is considered as a regulatory subunit that stabilizes the core complex [9]. RBM15 and its paralogue RBM15B can bind the m^{6}A methylation complex and recruit it to specific sites, resulting in the methylation of adenosine nucleotides in m^{6}A consensus motifs [38]. VIRMA recruits other methyltransferases to guide regioselective methylation and mediates preferential mRNA methylation in 3' UTRs and near stop codons [39]. ZC3H13 is an essential component for the translocation of WTAP, Virilizer and Hakai to the cytoplasm, which drives ZC3H13-WTAP-Virilizer-Hakai complex formation [40]. METTL16 contains a

methyltransferase domain furnished with an extra N-terminal module, which forms a deep groove that is vital for RNA binding. METTL16 independently catalyzes m^{6}A modification of U6 small nuclear RNA (snRNA) and a small number of mRNAs and non-coding RNAs [41–44]. In addition, ZCCHC4 plays a vital role in modifying human 28S rRNA and also interacts with a subset of mRNAs [45]. METTL5 is a recently reported m^{6}A RNA methyltransferase with a significantly different RNA-binding mode from others. It catalyzes m^{6}A modification of the 18S rRNA [46]. In addition to their well-known role in m^{6}A RNA methylation, recent studies have shown that m^{6}A methyltransferases have methyltransferase-independent functions [47, 48]. For instance, METTL3 and METTL16 have been shown to promote translation in the cytosol, independent of their methyltransferase activity [49, 50]. Similarly, METTL16 has been found to be involved in regulating DNA damage, regardless of their methyltransferase activity [51]. These findings highlight the complexity of m^{6}A regulation and suggest that there may be additional, as yet undiscovered, functions of m^{6}A methyltransferases beyond their traditional role in RNA methylation.

2.2 | m^{6}A erasers

m^{6}A demethylases can remove m^{6}A methylation and affect the function of m^{6}A modification in a dynamic, rapid, and signal-dependent manner (Figure 1) [7]. Unlike the m^{6}A methyltransferase and m^{6}A-binding protein groups, only FTO and ALKBH5 have been identified as m^{6}A demethylases. FTO, the first demethylase discovered, has efficient oxidative demethylation activity. It works with methyltransferase components to determine the modification status of mRNAs [52, 53]. FTO-mediated RNA m^{6}A demethylation is not specific. It also occurs with the cap 2-O-dimethyl adenosine (m^{6}A$_m$) modification of mRNAs, internal m^{6}A modification of U6 RNA, internal and cap m^{6}A$_m$ modification of snRNAs, and N^1-methyladenosine (m^{1}A) modification of tRNAs [54]. FTO can influence mRNA processing mediated by m^{6}A through binding the intronic regions of pre-mRNAs in the proximity of alternatively spliced exons and poly(A) sites [52]. ALKBH5, the second demethylase to be discovered, has profound effects on mRNA export and the assembly of mRNA processing factors in nuclear speckles [11]. Another study revealed that ALKBH5-directed m^{6}A demethylation is critical for correct splicing and the production of longer 3'-UTR mRNAs [55].

2.3 | m^{6}A readers

The recruitment of m^{6}A-specific binding proteins is the main mechanism by which m^{6}A modification affects the fate of RNAs. m^{6}A "readers" can recognize and bind m^{6}A sites, thereby mediating a series of biological changes, such as RNA degradation, processing, splicing and translation (Figure 1) [56]. YT521-B homology (YTH) RNA-binding domain is highly conserved and has an exquisite pocket for specific recognition of the m^{6}A [57]. YTH domain-containing protein 1 (YTHDC1) as a nuclear m^{6}A reader can influence mRNA splicing and nuclear export [13, 14]. YTHDC2 plays critical roles during spermatogenesis by accelerating both translation and decay of mRNA [24]. YTH domain-containing family proteins (YTHDFs) accelerate the metabolism of m^{6}A-modified mRNAs in the cytoplasm. YTHDF1 increases the translation efficiency of m^{6}A-modified mRNAs, and YTHDF2 selectively recognizes m^{6}A-modified mRNAs that promote their degradation [15, 16]. YTHDF3 promotes protein production through its interaction with YTHDF1 and affects methylated mRNA decay mediated through YTHDF2 [58]. Studies have shown that YTHDFs contain a high degree of functional redundancy. This functional redundancy is important for allowing YTHDFs to recognize and bind to a wide variety of m^{6}A-modified RNAs [59]. In addition, insulin-like growth factor 2 mRNA-binding proteins 1, 2 and 3 (IGF2BP1/2/3), as a family of m^{6}A readers, can recognize thousands of mRNA transcripts by identifying consistent GG(m^{6}A)C sequences [60]. IGF2BP1/2/3 can promote stability and facilitate translation efficiency in an m^{6}A-dependent manner [60–63]. Heterogeneous nuclear ribonucleoproteins (HNRNPs) are abundant nuclear proteins that alter the secondary structure of m^{6}A-modified RNAs. To promote primary miRNA processing, HNRNPA2B1 directly binds a set of nuclear transcripts and interacts with the microprocessor complex protein DiGeorge syndrome critical region 8 (DGCR8) [17]. Importantly, HNRNPC and HNRNPG can affect the abundance and alternative splicing of target mRNAs [18, 64]. Furthermore, eukaryotic initiation factor 3 (eIF3) binds m^{6}A sites in the 5' UTRs of mRNAs and promotes their cap-dependent translation [65].

3 | ROLES OF m^{6}A METHYLATION IN CANCER PROGRESSION

3.1 | m^{6}A methylation and cancer metabolic reprogramming

Tumorigenesis and progression are closely linked to the metabolic reprogramming of cancer cells. The reprogramming of energy metabolism promotes rapid cell growth, survival, proliferation, and long-term maintenance, and is considered a hallmark of tumor cells [66, 67].

Unlike normal differentiated cells, most cancer cells undergo metabolic reprogramming to accelerate aerobic

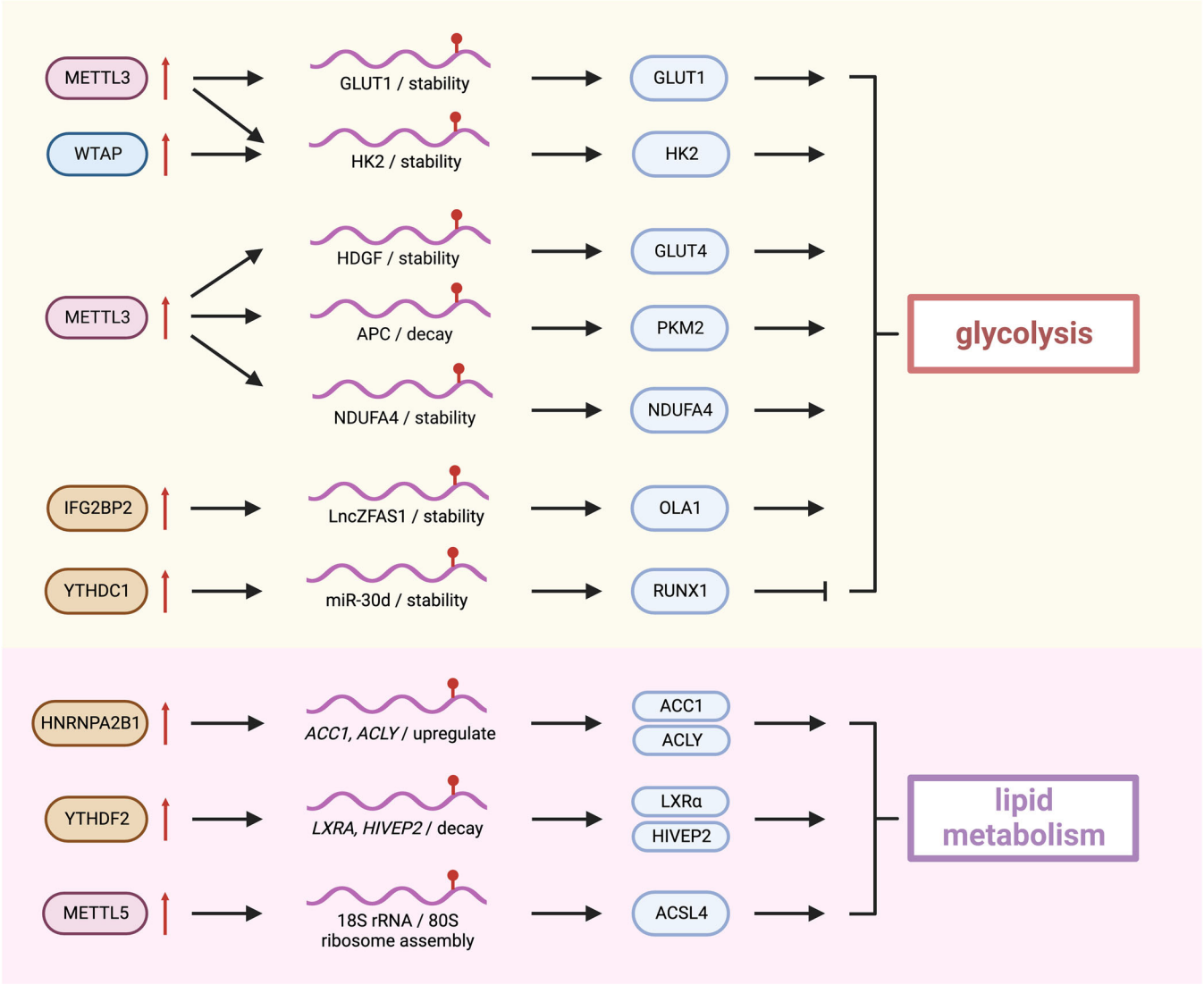

FIGURE 2 m^{6}A methylation and metabolic reprogramming. m^{6}A methylation can influence glycolysis and lipid metabolism by regulating a number of key metabolic enzymes and other factors.
Abbreviations: hnRNPA2B1, heterogeneous nuclear ribonucleoproteins A2/B1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; METTL3, methyltransferase-like 3; METTL5, methyltransferase-like 5; WTAP, Willms tumor 1 associated protein; YTHDC1, YTH domain containing protein 1; YTHDC2, YTH domain containing protein 2.

glycolysis for cellular processes, even under non-hypoxic conditions. This unique metabolic property is known as the "Warburg effect" [68, 69]. Increasing evidence suggests that m^{6}A methylation can regulate a number of key metabolic enzymes, thereby influencing the Warburg effect (Figure 2 and Table 1) [70]. The initial and crucial step of glucose metabolism is catalyzed by hexokinase 2 (HK2). In colorectal cancer (CRC), METTL3 has been observed to stabilize the expression of HK2 and glucose transporter type 1 (GLUT1) through an m^{6}A-IGF2BP2/3-dependent mechanism, thereby activating the subsequent glycolysis pathway and regulating tumor growth [71]. In cervical cancer, METTL3 has been found to target the 3'-UTR of HK2 mRNA and recruit the m^{6}A reader YTHDF1, which enhances the stability of HK2, ultimately promoting the Warburg effect [72]. Meanwhile, WTAP facilitates the Warburg effect of gastric cancer (GC) by enhancing the stability of HK2 mRNA [73]. Furthermore, METTL3 has been found to induce m^{6}A modification of hepatoma-derived growth factor (HDGF) mRNA. The m^{6}A reader IGF2BP3 recognizes the m^{6}A site on HDGF mRNA, thereby enhancing the stability of HDGF mRNA. This activation, in turn, promotes glycolysis and tumor angiogenesis in GC by stimulating GLUT4 and enolase 2 (ENO2) expression [74]. Furthermore, METTL3 could increase the m^{6}A level of APC mRNA and the m^{6}A reader YTHDF2 to promote

TABLE 1 Roles of m^{6}A methylation in cancer progression.

Cancer progression	Regulator	Cancer type	Mechanisms	Functions	Reference
Cancer metabolic reprogramming	METTL3	CRC	Stabilize HK2 and GLUT1	Enhance aerobic glycolysis and tumor progression	[71]
	METTL3	CC	Stabilize HK2	Enhance aerobic glycolysis and tumor progression	[72]
	WTAP	GC	Stabilize HK2	Enhance aerobic glycolysis and tumor progression	[73]
	METTL3	GC	Stabilize HDGF	Enhance aerobic glycolysis, angiogenesis, tumor growth and liver metastasis	[74]
	METTL3	ESCC	Facilitate APC decay	Enhance aerobic glycolysis and tumor progression	[75]
	IGF2BP2	CRC	Stabilize LncZFAS1	Enhance aerobic glycolysis and tumor progression	[76]
	METTL3	GC	Stabilize NDUFA4	Enhance aerobic glycolysis, mitochondrial fission and tumor progression	[77]
	YTHDC1	PDAC	Stabilize miR-30d	Suppress aerobic glycolysis and tumorigenesis	[78]
	HNRNPA2B1	ESCC	Promote the expression of ACLY and ACC1	Enhance fatty acid synthesis and tumor progression	[83]
	YTHDF2	GBM	Facilitate LXRA and HIVEP2 decay	Increased cellular cholesterol and enhance tumor progression	[84]
	METTL5	HCC	Facilitate 18S rRNA m^{6}A modification and 80S ribosome assembly	Enhance fatty acid metabolism and tumor progression	[85]
Cancer programmed cell death	METTL3	AML	Facilitate c-MYC, BCL2 and PTEN translation	Suppress apoptosis and enhance leukemia progression	[88]
	IGF2BP3	AML	Stabilize RCC2	Suppress apoptosis and enhance leukemia progression	[89]
	METTL3	LUAD	Facilitate FBXW7 translation	Suppress apoptosis and enhance tumor progression	[90]
	YTHDF2	TNBC	Stabilize several mRNAs in MAPK/ERK signaling pathways	Suppress apoptosis and enhance tumor progression	[91]
	YTHDF1	HCC	Facilitate ATG2A and ATG14 translation	Enhance autophagy and tumor progression	[93]
	FTO	CRC	Stabilize ATF4	Enhance pro-survival autophagy	[94]
	FTO	OSCC	Facilitate eIF4G1 decay	Suppress autophagy and enhance tumor progression	[95]
	METTL14	BC	Stabilize FGFR4	Suppress ferroptosis and confer anti-HER2 resistance	[97]
	METTL3	HB	Stabilize SLC7A11	Suppress ferroptosis and enhance tumor progression	[98]
	FTO	PTC	Inhibit SLC7A11 translation	Suppress ferroptosis and enhance tumor progression	[99]
Cancer metastasis	IGF2BP2	HNSCC	Stabilize slug	Enhance lymphatic metastatic	[104]
	YTHDC1	TNBC	Promote the nuclear export of SMAD3	Enhance lung metastasis	[105]
	METTL3	GC	Stabilize ZMYM1	Enhance EMT process and metastasis	[106]
	ALKBH5	NSCLC	Inhibit YAP expression and activity	Inhibit tumor growth and metastasis	[107]
	METTL14	CRC	Facilitate SOX4 decay	Enhance EMT process and metastasis	[108]
	YTHDF3	BC	Facilitate ST6GALNAC5, GJA1 and EGFR translation	Enhance angiogenesis and tumor brain metastasis	[109]
	METTL3	LC	Felicitate miR-143-3p biogenesis	Enhance angiogenesis and tumor brain metastasis	[110]
	METTL14	TSCC	Inhibit BATF2 expression	Suppress angiogenesis and tumor metastasis	[111]

Abbreviations: ALKBH5, alkB homolog 5; AML, acute myeloid leukemia; BC, breast cancer; CC, Cervical cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; FTO, fat mass and obesity-associated protein; GBM, glioblastoma; GC, gastric cancer; HB, hepatoblastoma; HCC, hepatocellular carcinoma; hnRNPA2B1, heterogeneous nuclear ribonucleoproteins A2/B1; HNSCC, head and neck squamous cell carcinoma; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; LC, lung cancer; LUAD, lung adenocarcinoma; METTL14, methyltransferase-like 14; METTL3, methyltransferase-like 3; METTL5, methyltransferase-like 5; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; PTC, papillary thyroid carcinoma; TNBC, triple negative breast cancer; TSCC, tongue squamous cell carcinoma; WTAP, Willms tumor 1 associated protein; YTHDC1, YTH domain-containing protein 1; YTHDC2, YTH domain-containing protein 2; YTHDFs, YTH domain-containing family proteins

APC mRNA degradation in esophageal squamous cell carcinoma (ESCC) cells. Reduced APC increases the expression of pyruvate kinase M2 (PKM2), thereby leading to enhanced aerobic glycolysis [75]. In addition to influencing these key metabolic enzymes in glycolysis, m^{6}A modifications can also regulate several proteins and non-coding RNAs related to the glycolysis involved in tumor progression. In CRC, IGF2BP2 as an m^{6}A reader stabilizes long non-coding RNA (lncRNA) zinc finger antisense 1 (ZFAS1) [76]. Then ZFAS1 directly binds to obg-like ATPase 1 (OLA1) to enhance the ATPase activity of OLA1, which enhances the ATP hydrolysis capacity and activates the Warburg effect [76]. In GC cells, it has been demonstrated that METTL3 promotes the methylation of NADH:ubiquinone oxidoreductase subunit A4 (NDUFA4) mRNA, which is stabilized by IGF2BP1 [77]. This leads to increased NDUFA4 expression, promoting GC development by enhancing glycolysis and mitochondrial fission [77]. However, it is worth noting that m^{6}A methylation can also suppress aerobic glycolysis. In pancreatic ductal adenocarcinoma, the m^{6}A reader YTHDC1 facilitates the maturation of miR-30d through m^{6}A-mediated regulation of mRNA stability [78]. Subsequently, miR-30d induces the downregulation of SLC2A1 and HK1 by directly targeting runt-related transcription factor 1 (RUNX1), which ultimately inhibits the Warburg effect [78]. Numerous studies have demonstrated that the tumor glucose aerobic glycolytic pathway holds great potential as a target for tumor therapy [79, 80]. Additionally, it has been revealed that m^{6}A methylation plays a significant role in the process of tumor metabolic reprogramming [76, 81]. Therefore, targeting m^{6}A-related regulators may be a promising approach to regulate metabolic reprogramming in the future.

In addition to glucose metabolism, fatty acid oxidation is an extremely relevant energy source for tumor cells [82]. Recently, reports have indicated that m^{6}A modifications regulate lipid metabolism to support tumor progression [83] (Figure 2 and Table 1). In ESCC, ATP citrate lyase (ACLY) and acetyl-CoA carboxylase 1 (ACC1), the de novo fatty acid synthetic enzymes, can be upregulated by HNRNPA2B1, thus accelerating cellular lipid accumulation, which contributes to tumor growth and metastasis [83]. In glioblastoma, YTHDF2 depletion decreases cellular cholesterol levels and inhibits cell proliferation, invasion, and tumorigenesis [84]. This is because YTHDF2 can mediate m^{6}A-dependent mRNA decay to restrain liver X receptor alpha (LXRA) and human immunodeficiency virus type I enhancer binding protein 2 (HIVEP2) expression [84]. Moreover, in hepatocellular carcinoma (HCC), METTL5 has been shown to promote both de novo lipogenesis and β-oxidation, which contribute to cancer growth and progression [85]. The mechanism behind this involves the depletion of METTL5-mediated 18S rRNA m^{6}A modification, which impairs 80S ribosome assembly and decreases the translation of acyl-CoA synthetase (ACSL) family mRNAs in HCC cells [85]. The aforementioned discoveries highlight the crucial connections between m^{6}A modification and fatty acid metabolism, underscoring their fundamental physiological roles in tumorigenesis. Hence, disrupting fatty acid metabolism that depends on m^{6}A methylation could provide novel approaches for anti-tumor therapies.

3.2 | m^{6}A methylation and cancer programmed cell death

Programmed cell death, which encompasses apoptosis, autophagy, pyroptosis, necroptosis, and ferroptosis, has been found to play a critical role in tumorigenesis, the tumor microenvironment, and cancer treatment [86]. In recent years, several studies have linked m^{6}A modification to various programmed cell death processes (Figure 3 and Table 1) [87]. For example, in myeloid leukemia cell lines, depletion of METTL3 inhibits the translation of c-MYC, B-cell lymphoma 2 (BCL-2) and phosphatase and tensin homolog (PTEN) mRNAs, which markedly induces cell differentiation and increases levels of apoptosis [88]. However, IGF2BP3 overexpression can have the opposite effect, dramatically suppressing apoptosis and promoting the proliferation and tumorigenesis of acute myeloid leukemia (AML) by stabilizing the regulator of chromosome condensation 2 (RCC2) mRNA in an m^{6}A-dependent manner [89]. Dysregulation of METTL3 can also affect the apoptosis and proliferation phenotype of lung adenocarcinoma cells. Specifically, METTL3 contributes to the m^{6}A modification of the coding region of F-box and WD repeat domain-containing 7 (FBXW7) mRNA, which enhances FBXW7 translation and decreases the protein levels of Mcl-1 and c-Myc, ultimately leading to decreased proliferation and increased apoptosis [90]. Interestingly, in MYC-driven breast cancer, YTHDF2 can stabilize several mRNAs in mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathways and cause endoplasmic reticulum stress through unfolded protein accumulation, contributing to an apoptotic phenotype [91].

Autophagy is a highly conserved catabolic process that involves salvaging and reusing degraded proteins, lipids, and organelles through the lysosomal degradation pathway [92]. Recent studies have linked m^{6}A-induced autophagy to increased tumor cell migration and invasion. Under hypoxic conditions, hypoxia-inducible factor 1 alpha (HIF-1α) can upregulate the YTHDF1 transcription by directly binding to its promoter region. YTHDF1 can

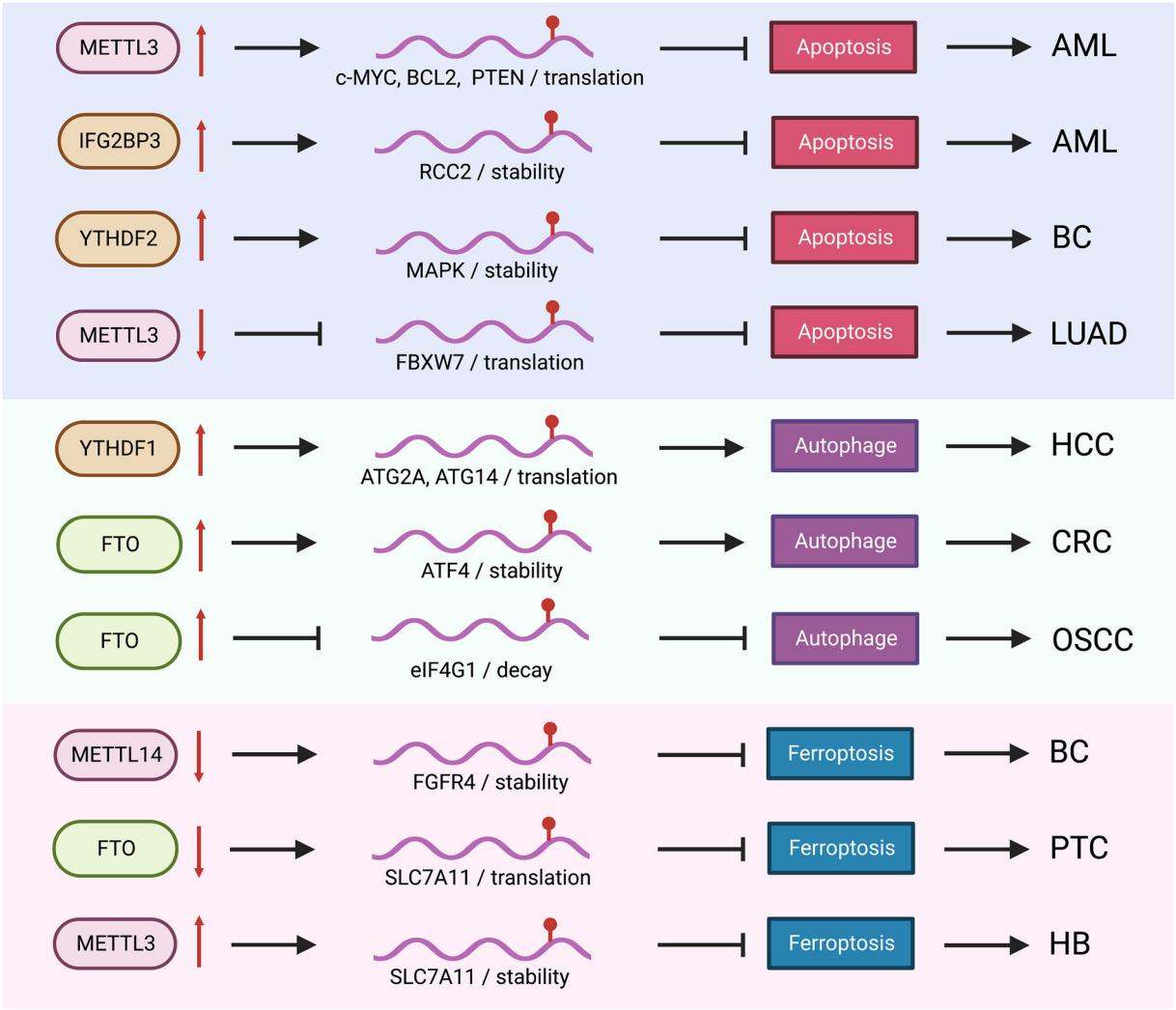

FIGURE 3 m^6A methylation and programmed cell death. m^6A methylation can influence the initiation and progression of various cancers via influencing apoptosis, autophagy, and ferroptosis processes.
Abbreviations: AML, acute myeloid leukemia; BC, breast cancer; CRC, colorectal cancer; FTO, fat mass and obesity-associated protein; HB, hepatoblastoma; HCC, hepatocellular carcinoma; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; LUAD, lung adenocarcinoma; METTL14, methyltransferase-like 14; METTL3, methyltransferase-like 3; OSCC, oral squamous cell carcinoma; PTC, papillary thyroid carcinoma; YTHDC1, YTH domain-containing protein 1; YTHDC2, YTH domain-containing protein 2.

promote the translation of autophagy related 2A (ATG2A) and ATG14, which facilitates autophagy and autophagy-related malignancy in HCC [93]. In CRC, during glutaminolysis inhibition, upregulation of FTO stabilizes activating transcription factor 4 (ATF4) mRNA by reducing its m^6A modification [94]. This results in the upregulation of DNA damage-inducible transcript 4 (DDIT4) expression, which in turn leads to the inactivation of mammalian target of rapamycin (mTOR) signaling and induces a pro-survival autophagy response [94]. On the contrary, another study has reported that m^6A-induced autophagy has a negative relationship with tumorigenesis. In oral squamous cell carcinoma cells, knockdown of FTO can enhance autophagic flux and inhibit malignant progression by promoting eukaryotic initiation factor 4 gamma 1 (eIF4G1) mRNA degradation in an m^6A-YTHDF2-dependent manner [95].

Ferroptosis is a novel form of non-apoptotic cell death that is driven by iron-dependent lipid peroxidation [96]. Researches have shown that m^6A modification is closely associated with ferroptosis. For example, in breast cancer, fibroblast growth factor receptor 4 (FGFR4) accelerates cystine uptake and $Fe2^+$ efflux via the β-catenin/transcription factor 4 (TCF4)-SLC7A11/ferroportin 1 (FPN1) axis, which confers anti-human epidermal growth factor receptor 2 (HER2) resistance in part by suppressing ferroptosis. Knockdown of METTL14 promotes FGFR4 mRNA stability

and upregulates its expression [97]. In hepatoblastoma, METTL3-mediated m^{6}A modification enhances SLC7A11 stability and expression in an m^{6}A-IGF2BP1-dependent manner [98]. SLC7A11 promotes tumorigenesis by enhancing ferroptosis resistance [98]. In addition, FTO inhibits the development of prevents papillary thyroid carcinoma by downregulating the expression of SLC7A11 through ferroptosis [99].

Despite several studies showing that m^{6}A modification is critical to programmed cell death, its potential molecular mechanisms in cancer have not been fully established. Therefore, deciphering the m^{6}A and programmed cell death signaling pathways in various cancers is imperative, as it not only provides new insights into the pathogenesis but also helps in the development of new targeted anticancer therapeutic strategies.

3.3 | m^{6}A methylation and cancer metastasis

Metastasis is the leading cause of poor prognosis in cancer patients [100]. Recent studies have demonstrated that m^{6}A methylation is associated with tumor invasion and metastasis by regulating epithelial-mesenchymal transition (EMT) states [101] and angiogenesis (Table 1) [102].

EMT is a crucial developmental process wherein cells lose epithelial polarization and gain mesenchymal features and is closely related to tumor metastasis [103]. For example, in head and neck squamous cell carcinoma, EMT enhances cell motility and invasiveness, promoting the lymphatic metastatic process by regulating snail family zinc finger 2 (Snai2) mRNA stability, a key EMT-related transcription factor, in an m^{6}A modification-dependent manner [104]. Additionally, YTHDC1 promotes the nuclear export of methylated SMAD family member 3 (SMAD3) mRNA, affecting its protein production and leading to enhanced EMT and promoting lung metastasis of triple-negative breast cancer (TNBC) cells [105]. In GC, METTL3 facilitates the EMT process and metastasis by enhancing the stability of zinc finger MYM type-containing 1 (ZMYM1) via the m^{6}A reader human antigen R (HuR), which mediates the repression of E-cadherin by recruiting the C-terminal binding protein (CtBP)/ lysine-specific demethylase 1 (LSD1)/co-repressor for element-1-silencing transcription factor (CoREST) complex [106]. Conversely, in non-small cell lung cancer (NSCLC), the m^{6}A demethylase ALKBH5 can reduce YTHDF-mediated YAP expression and inhibit miR-107/ large tumor suppressor kinase 2 (LATS2)-mediated YAP activity, thereby inhibiting tumor growth and metastasis [107]. Overexpression of METTL14 markedly inhibits the EMT process and CRC cell metastasis by repressing SRY-box transcription factor 4 (SOX4) expression through YTHDF2-dependent mRNA degradation. Furthermore, it can elevate the expression of N-cadherin and Vimentin, while reducing E-cadherin expression levels [108].

Angiogenesis plays a prominent role in the development and metastasis of tumors. In patients who have breast cancer with brain metastasis, YTHDF3 promotes cancer cell interactions with brain endothelial cells and astrocytes, blood-brain barrier extravasation, angiogenesis, and outgrowth [109]. Mechanistically, YTHDF3 mediates multiple steps of brain metastasis, primarily by enhancing the translation of m^{6}A-enriched transcripts for ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 5 (ST6GALNAC5), gap junction alpha-1 protein (GJA1), and epidermal growth factor receptor (EGFR), all of which are associated with brain metastasis [109]. Furthermore, it has been shown that Mettl3, an m^{6}A methyltransferase, can enhance the splicing of precursor miR-143-3p, facilitating its biogenesis. This, in turn, leads to activation of the miR-143-3p/vasohibin-1 (VASH1) axis, which promotes brain metastasis of lung cancer by regulating angiogenesis and microtubules and increasing the degradation of vascular endothelial growth factor A (VEGFA) [110]. In addition, METTL14-mediated m^{6}A modification has been shown to negatively regulate the mRNA expression of basic leucine zipper ATF-like transcription factor 2 (BATF2), and suppress growth, metastasis and angiogenesis of tongue squamous cell carcinoma (TSCC) by inhibiting VEGFA [111].

While a growing number of studies have evaluated the role of m^{6}A methylation in tumor metastasis, it is important to recognize that this is a complex biological process. The specific role of m^{6}A methylation modifications in the development of primary tumor cells and their subsequent metastasis requires further investigation to gain a deeper understanding of the underlying mechanisms.

4 | m^{6}A METHYLATION IMPLICATIONS FOR CANCER THERAPY

4.1 | m^{6}A methylation and cancer therapeutic resistance

Therapeutic resistance is a well-known phenomenon in cancer treatment and has become a significant hurdle to overcome in the management of tumor patients. There are multiple mechanisms that contribute to therapeutic resistance in cancer, including specific genetic and epigenetic changes in the cancer cell and its microenvironment [112]. Recently, m^{6}A methylation has emerged as a novel epigenetic regulatory mechanism that plays a crucial role in the progression of drug resistance. A growing body

of evidence suggests that m^{6}A methylation is closely associated with chemoresistance, radio-resistance, and resistance to immunotherapy in cancer [113].

m^{6}A methylation mediates the development of resistance to many classical chemotherapeutic agents, such as cisplatin [114–118], 5-fluorouracil (5-FU) [119, 120] and gemcitabine [121–123]. In NSCLC, the writer METTL3 and the reader YTHDF1 play distinct roles in rendering cancer cells resistant to cisplatin treatment [114]. While METTL3 enhances sensitivity to cisplatin by increasing YAP expression and activity, it has also been found to promote YAP mRNA translation through the recruitment of YTHDF1/3 and eIF3b to the translation initiation complex. In addition, METTL3 regulates the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)-miR-1914-3p-YAP axis, which leads to increased YAP mRNA stability [114]. Depletion of YTHDF1 mediates cisplatin resistance through the kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid 2-related factor 2 (NRF2)/aldo-keto reductase family 1 member C1 (AKR1C1) axis, and higher expression of YTHDF1 is correlated with better clinical outcomes in NSCLC patients [115]. High levels of ALKBH5 contribute to cisplatin resistance in oral squamous cell carcinoma by demethylating forkhead box M1 (FOXM1) and the nanog homeobox protein (NANOG) nascent transcript [117]. Similarly, the ALKBH5-homeobox A10 (HOXA10) loop promotes cancer cell cisplatin resistance by demethylating janus kinase 2 (JAK2) in epithelial ovarian cancer [118]. Upregulation of METTL3 in CRC cells increases the expression of lactate dehydrogenase A (LDHA) to promote glucose metabolism-mediated 5-FU resistance and tumor progression [119]. In pancreatic cancer, an m^{6}A-dependent mechanism promotes gemcitabine resistance by regulating the lncANRIL splicing process [121]. Additionally, METTL14 promotes gemcitabine resistance by regulating the stability of cytidine deaminase transcripts [122].

Radiotherapy is a type of ionizing irradiation that works by damaging cancer cells' DNA, which can cause them to stop dividing or die. In glioblastoma multiforme, research has shown that METTL3-dependent m^{6}A modification is critical for glioblastoma stem cell (GSC) maintenance and radiation sensitivity [124]. High levels of METTL3 have been found to induce radio-resistance in GSCs through SOX2-dependent enhanced DNA repair [124]. Furthermore, studies have revealed that ALKBH5 can alter DNA damage repair and radiation sensitivity by regulating several homologous recombination genes in GSCs [125]. Additionally, YTHDC2 has been shown to promote radiotherapy resistance in nasopharyngeal carcinoma cells by activating the insulin-like growth factor 1 receptor (IGF1R)/protein kinase B (ATK)/ribosomal protein S6 (S6) signaling axis [126]. In hypopharyngeal squamous cell carcinoma, METTL3 mediates the m^{6}A methylation of circCUX1, which stabilizes its expression and confers radio-resistance through the caspase-1 pathway [127].

In recent years, tumor immunotherapy has become a hot spot in the field of oncology treatment. Although immunotherapy is regarded as a promising approach to combat cancer, the occurrence of immune evasion limits its effectiveness. In CRC, when METTL3 is silenced, there is a reduction in the accumulation of myeloid-derived suppressor cells (MDSCs) [128]. This reduction promotes the activation and proliferation of CD4$^+$ and CD8$^+$ T cells. Mechanistically, METTL3 promotes basic helix-loop-helix family member e41(BHLHE41) expression in an m^{6}A-dependent manner. This promotion of BHLHE41 expression subsequently induces C-X-C motif chemokine ligand 1 (CXCL1) transcription, which enhances MDSC migration in vitro [128]. In melanoma and CRC, ALKBH5 deficiency reduces monocarboxylate transporter 4 (Mct4) expression and lactate content of the tumor microenvironment and the composition of tumor-infiltrating Treg and myeloid-derived suppressor cells [129]. Intriguingly, FTO plays a critical role in regulating the immune surveillance that tumors use to evade detection. FTO-mediated m^{6}A demethylation in tumor cells results in increased levels of transcription factors such as c-Jun, JunB, and CCAAT/enhancer-binding protein beta (C/EBPβ) [130]. This enhancement promotes glycolysis in tumors and also reduces T cell effector functions [130]. Moreover, in melanoma, the knockdown of FTO has been shown to sensitize melanoma cells to interferon-gamma (IFN-γ) and increase their sensitivity to anti-programmed cell death protein 1 (PD-1) treatment [131].

Overall, further research to understand the mechanisms of m^{6}A modification in the development of therapy resistance is particularly important, which can improve the clinical outcomes of cancer patients.

4.2 | m^{6}A methylation and cancer targeted therapy

Current research demonstrates that RNA m^{6}A modification is involved in tumorigenesis and development, and some related essential regulators have been used as new pharmacological targets for anti-tumor drug development [132]. The RNA m^{6}A demethylase FTO is a member of the 2-oxoglutarate (2OG) and iron-dependent nucleic acid oxygenase (NAOX) family. Analyzing the substrate specificity and catalytic domain of FTO provides a new way to develop highly specific and efficient inhibitors [133, 134]. The first FTO inhibitor was rhein, which globally increased the cellular mRNA m^{6}A levels by binding the FTO catalytic domain and preventing the recognition of

m^{6}A substrates [135]. However, rhein shows little selectivity for the alkB family demethylases [136]. Meclofenamic acid (MA), a non-steroidal anti-inflammatory drug, is a highly selective inhibitor of FTO that specifically inhibits FTO over ALKBH5. MA2 is an ester derivative of MA that might aid the inhibitor in penetrating cells [137]. Of note, the FTO inhibitor MA2 dramatically inhibits the growth and self-renewal of GSCs. Consistent with the effect on GSCs, in mice treated with MA2, the growth of tumors was shown to be slowed, and survival was significantly prolonged [138]. Furthermore, MO-I-500 acts as a pharmacological inhibitor of FTO and could effectively inhibit cell survival and/or colony formation in a TNBC cell line [139]. R-2-hydroxyglutarate (R-2HG), a metabolite produced by the mutant isocitrate dehydrogenase 1/2 (IDH1/2) enzyme, plays an anti-tumor role in leukemia by inhibiting cell proliferation and promoting cell cycle arrest and apoptosis [140]. Mechanistically, R-2HG directly targets the m^{6}A demethylase FTO and inhibits its catalytic activity, increasing the level of m^{6}A-modified RNA in R-2HG-sensitive leukemia cells. In addition, the effects of R-2HG on the treatment of leukemia were improved when it was used in combination with various first-line anticancer drugs, including all-trans retinoic acid (ATRA), azacitidine, decitabine and daunorubicin [140, 141]. FB23 and FB23-2 are two newly discovered small-molecule inhibitors of FTO based on structure-guided design that directly bind to FTO and selectively inhibit FTO's m^{6}A demethylase activity [142]. Moreover, FB23-2 suppresses leukemia progression and prolongs survival. FB23-2 also displays therapeutic efficacy in targeting a patient-derived xenograft AML mouse model [142]. Additionally, CS1 and CS2 are highly efficacious FTO inhibitors screened from the 260,000 compounds [143]. They can selectively bind to and occupy the catalytic pocket of FTO, thus inhibiting FTO's demethylase activity. Surprisingly, CS1 and CS2 exhibit strong anti-tumor effects in multiple types of cancers, and they are highly feasible for clinical application [143].

In addition to FTO inhibitors, several studies have shown that other m^{6}A protein inhibitors may be promising targets for treating m^{6}A-related human cancers. ALK-04, a specific inhibitor of ALKBH5, enhances the efficacy of immunotherapy in combination with GVAX and PD-1 antibodies [129]. The first-in-class catalytic inhibitor of METTL3, STM2457, is a highly potent and selective inhibitor. Its in vivo activity and therapeutic efficacy represent a significant milestone, as it is the first demonstration of an RNA methyltransferase inhibitor's effectiveness against cancer [144]. BTYNB, a novel IGF2BP1 inhibitor, suppresses the cell cycle and cancer progression by impairing IGF2BP1-dependent stabilization of mRNA-encoding factors. Moreover, BTYNB acts in an additive manner or even synergistically with palbociclib, a cell cycle inhibitor targeting key E2 promoter binding factor (E2F)-activating kinases [145, 146]. The small-molecule inhibitor CWI1-2 has been shown to effectively bind to IGF2BP2 and inhibit its interaction with m^{6}A-modified target transcripts. This is a promising development, as CWI1-2 has been shown to have significant anti-leukemia effects both in vitro and in vivo. Additionally, it has been found to exhibit synergistic effects when used in combination with other AML therapeutic agents such as daunorubicin and homoharringtonine [147].

Collectively, these results reveal that targeting m^{6}A methylation enzymes is a promising approach for anticancer therapy. However, it is important to note that current m^{6}A methylation inhibitors alter the overall level of m^{6}A methylation by targeting the enzymes responsible for this process. It remains unclear whether targeting gene-specific m^{6}A methylation will lead to better therapeutic outcomes. Further research is needed to explore this possibility.

5 | m^{6}A METHYLATION IN IMMUNITY AND IMMUNOTHERAPY

5.1 | m^{6}A methylation and cancer immunity

m^{6}A modification not only regulates the fate of tumor cells by targeting specific genes in various cancers but also affects the anti-tumor functions of immune cells. Recent studies have highlighted the critical role of m^{6}A methylation in tumor immunity [128, 148]. These findings suggest that m^{6}A methylation may represent a promising target for developing novel immunotherapeutic strategies to enhance anti-tumor immunity and improve the outcomes of cancer treatment.

Natural killer (NK) cells are the prototypical innate lymphoid immune cells and play a vital role in tumor surveillance [149]. Recently, researchers have found that YTHDF2 is required for NK cell survival, proliferation, and effector functions [150]. Deletion of YTHDF2 was found to significantly inhibit interleukin-15 (IL-15)/signal transducer and activator of transcription 5 (STAT5) signaling in activated NK cells, which downregulated STAT5 activation, thereby impairing NK cells anti-tumor and antiviral activity. YTHDF2 can also inhibit the mRNA stability of transactive response DNA binding protein (Tardbp), regulating NK cells proliferation and division [150]. In addition, one study showed that METTL3-mediated mRNA m^{6}A methylation promotes the anti-tumor immunity of NK cells [151]. Mechanistically, METTL3 can promote src homology 2 domain-containing protein tyrosine phosphatase-2

(SHP-2) expression, AKT-mTOR and MAPK-ERK signaling pathways, leading NK cells to respond to IL-15 [151].

Tumor-associated macrophages (TAMs) can polarize into classically activated macrophages with anti-tumor responses (M1 type) or alternatively activated macrophages with pro-tumor functions (M2 type), contributing to dynamic and heterogeneous tumor immunity [152, 153]. Studies have shown that m^{6}A methylation can regulate the polarization of macrophages in multiple ways. Overexpression of METTL3 greatly facilitates M1 macrophage polarization by upregulating STAT1 expression through enhancing mRNA stability [154]. FTO knockdown impedes macrophage activation by inhibiting the nuclear factor kappa B (NF-κB) signaling pathway and reducing the mRNA stability of STAT1 and peroxisome proliferator-activated receptor gamma (PPAR-γ) [155]. Deletion of METTL14 diminishes suppressor of cytokine signaling 1 (SOCS1) expression and leads to overactivation of toll-like receptor 4 (TLR4)/NF-κB signaling, which blunts the negative feedback control of macrophage activation in response to bacterial infection [156]. Moreover, the loss of METTL3 in macrophages has been found to establish an immunosuppressive microenvironment by increasing the infiltration of M1- and M2-like TAM and Treg cells in tumors [157]. This effect is mediated by the impairment of YTHDF1-mediated translation of sprouty-related EVH1 domain-containing protein 2 (SPRED2) and the subsequent downregulation of ERK, NF-κB and STAT3 phosphorylation [157]. IGF2BP2 can switch M1 macrophages to M2 activation by targeting tuberous sclerosis complex 1 (TSC1)-mechanistic target of rapamycin complex 1 (mTORC1) pathway and PPARγ-mediated fatty acid uptake [158].

Dendritic cells (DCs) are a critical component of the immune system and play a key role in stimulating T cell responses by presenting antigens [159]. Specifically, a recent study showed that Mettl3-mediated m^{6}A modification enhances the translational expression of CD80 and CD40, leading to increased antigen presentation and T-cell stimulation by DCs [160]. Additionally, Mettl3 promotes the translational expression of Tirap, which strengthens TLR4/NF-κB signaling and increases the secretion of proinflammatory cytokines [160]. Another study demonstrated that mRNA m^{6}A methylation and YTHDF1 in DCs control anti-tumor immunity [148]. Loss of YTHDF1 in classical DCs was found to enhance the cross-presentation of tumor antigens and the cross-priming of CD8$^+$ T cells, while YTHDF1 promotes the translation of lysosomal cathepsins for excessive antigen degradation [148].

T cells, as a key component of the adaptive immune system, play a central role in cancer immunology due to their ability to directly mediate cancer cell killing. mRNA m^{6}A modification has emerged as an important regulator of T cell homeostasis and differentiation. In mouse T cells, loss of Mettl3 has been shown to increase the half-lives and protein levels of Socs1, Socs3, and cytokine-inducible SH2-containing protein (Cish) mRNAs, which in turn suppresses the IL-7/STAT5 signaling pathway, ultimately disrupting T cell homeostatic proliferation and differentiation [161]. ALKBH5-mediated m^{6}A demethylation in CD4$^+$ T cells increases the transcript stability and protein expression of CXCL2 and IFN-γ, which controls the pathogenicity of CD4$^+$ T cells during autoimmunity [162]. Interestingly, tumor-intrinsic FTO restricts the activation and effector states of CD8$^+$ T cells. FTO knockdown impairs the glycolytic activity of tumor cells by elevating the transcription factors c-Jun, JunB, and C/EBPβ, which suppresses the function of CD8$^+$ T cells [130].

5.2 | m^{6}A methylation and cancer immunotherapy

In recent years, immune checkpoint blockade (ICB) therapy has led to a significant breakthrough in the treatment of various types of cancer. However, resistance to ICB remains a major challenge for the future of cancer treatment. To address this challenge, some research groups are exploring the potential of combining checkpoint blockade with m^{6}A inhibitors as a new therapeutic strategy to improve outcomes in patients with a low response to checkpoint blockade. This approach shows promise and may represent a significant step forward in the fight against cancer. The deletion of the m^{6}A RNA demethylase ALKBH5 has been found to increase the sensitivity of tumors to anti-PD-1 immunotherapy while decreasing the populations of MDSC and Treg suppressive immune cells [129]. The mechanism underlying this effect involves the inhibition of ALKBH5 mRNA demethylation, which increases m^{6}A in MCT4/SLC16A3, a lactate transporter. This, in turn, decreases the mRNA levels of MCT4/SLC16A3 and leads to a reduction in lactate in the tumor interstitial fluid [129]. Similarly, YTHDF1 depletion elevates the antigen-specific CD8$^+$ T cell anti-tumor response and enhances the therapeutic efficacy of programmed death ligand 1 (PD-L1) checkpoint blockade [148]. In melanoma, the level of FTO is significantly increased and reduces the response to PD-1-blocking immunotherapy [131]. Knockdown of FTO in mice has been shown to the m^{6}A methylation of the proto-oncogenes PD-1, C-X-C chemokine receptor type 4 (CXCR4), and SOX10, rendering melanoma cells more sensitive to interferon-gamma (IFN-γ) and improving the anti-PD-1 treatment response of melanoma in mice [131].

TABLE 2 Methodologies for detecting m^{6}A methylation.

Time	Method	Approach	Advantages	Limitations	Reference
2012	m^{6}A-seq	Anti-m^{6}A antibodies	Transcriptome-wide sequencing	Low resolution; nonspecific antibody binding	[3]
	MeRIP-seq	Anti-m^{6}A antibodies	Transcriptome-wide sequencing	Low resolution; nonspecific antibody binding	[4]
2015	PA-m^{6}A-seq	RNA-antibody photocrosslinking and immunoprecipitation	High resolution	Low cross-linking yield; nonspecific antibody binding	[164]
	miCLIP	RNA-antibody photocrosslinking and immunoprecipitation	Single-base resolution	Low cross-linking yield; nonspecific antibody binding	[6]
2016	m^{6}A-LAIC-seq	Anti-m^{6}A antibodies	Quantify m^{6}A stoichiometry	Low resolution; nonspecific antibody binding	[165]
2019	MAZTER-seq	MazF endoribonuclease	Single-base resolution	Low sensitivity; only apply to the RNA ACA motif	[166]
	m^{6}A-REF-seq	MazF endoribonuclease	Single-base resolution	Low sensitivity; only apply to the RNA ACA motif	[167]
	DART-seq	RNA-editing enzyme	Single-base resolution	High false-positive rates due to non-specific C-to-U editing events	[168]
2020	m^{6}A-SEAL	FTO-assisted m^{6}A selective chemical labeling	Good sensitivity, specificity	Low resolution; lack of stoichiometry information	[169]
	m^{6}A-label-seq	Metabolic allyl-labeling	Single-base resolution	Low labeling yield; lack of stoichiometry information	[170]
2022	m^{6}A-SAC-seq	Selective Allyl Chemical labeling	Low-input RNA; single-base resolution; with stoichiometry information	GAC context preference	[171]
	GLORI	Glyoxal and nitrite-mediated deamination	Single-base resolution; absolute quantification	High sequencing cost; improve the deamination rate	[172]

Abbreviations: 4SU, 4-thiouridine; APOBEC1, apolipoprotein B mRNA editing catalytic subunit 1; DART-seq, deamination adjacent to RNA modification targets; FTO, fat mass and obesity-associated protein; GLORI, glyoxal and nitrite-mediated deamination of unmethylated adenosines; m^{6}A-LAIC-seq, m^{6}A-Level and Isoform Characterization sequencing; m^{6}A-REF-seq, m^{6}A-sensitive RNA-endoribonuclease-facilitated sequencing; m^{6}A-SAC-seq, m^{6}A-selective allyl chemical labeling and sequencing; m^{6}A-SEAL, FTO-assisted m^{6}A selective chemical labeling method; m^{6}A-seq, N^6-methyladenosine–sequencing; MeRIP-seq, methylated RNA immunoprecipitation and sequencing; miCLIP, m^{6}A individual-nucleotide resolution cross-linking and immunoprecipitation; PA-m^{6}A-seq, photo-crosslinking-assisted m^{6}A sequencing; YTH YT521-B homology

In CRC and melanoma, depletion of methyltransferases, Mettl3 and Mettl14, can augment the response to anti-PD-1 treatment promoted by enhancing IFN-γ-Stat1-interferon regulatory factor 1 (Irf1) signaling through stabilizing the Stat1 and Irf1 mRNA via Ythdf2 [163].

6 | METHODOLOGIES FOR DETECTING m^{6}A METHYLATION

For a long time after the discovery of m^{6}A modification, quantifying and localizing it at the whole transcriptome level was challenging due to methodological limitations. However, recent years have witnessed significant progress in m^{6}A mapping and measurement techniques (Table 2).

In 2012, N^6-methyladenosine–sequencing (m^{6}A-seq) and methylated RNA immunoprecipitation and sequencing (MeRIP-seq), two similar m^{6}A antibody-dependent methods, were developed [3, 4]. These methods involve splitting RNA into fragments of around 200 nucleotides, enriching the m^{6}A-containing RNA fragments with m^{6}A antibodies, and sequencing them. While this approach can measure a large number of modification sites at the transcriptome level, it lacks precise location and stoichiometry information. Nevertheless, it remains the most widely used method for detecting m^{6}A modification [3, 4].

In 2015, photo-crosslinking-assisted m^{6}A sequencing (PA-m^{6}A-seq) and m^{6}A individual-nucleotide resolution cross-linking and immunoprecipitation (miCLIP) were developed [6, 164]. They performed an ultraviolet (UV) cross-linking step after anti-m^{6}A immunoprecipitation, which improved the resolution. PA-m^{6}A-seq, add 4-thiouridine (4SU) to strengthen cross-linking, improve the resolution, and further view the sequence of bases

within the 30-nt window. This technique can only detect m^{6}A near the site with 4SU operation, while the site far away cannot be detected [164]. miCLIP overcomes the distance limitation and can identify more m^{6}A sites with a guaranteed single-base resolution [6]. In addition, m^{6}A-level and isoform characterization sequencing (m^{6}A-LAIC-seq) can analyze m^{6}A levels across the entire transcriptome and quantify the ratio of m^{6}A-modified to non-methylated transcripts [165].

In 2019, two similar m^{6}A antibody-independent enzymatic methods, MAZTER-seq and m^{6}A-sensitive RNA-endoribonuclease-facilitated sequencing (m^{6}A-REF-seq), were developed [166, 167]. These methods are based on MazF RNase, which recognizes the unmethylated ACA motif of RNA and cleaves at that site, providing accurate and single-nucleotide resolution information about m^{6}A sites. However, one of the limitations of these methods is that they can only identify methylation at the ACA site, which accounts for only about 16% of the DRACH (D = A/G/U, R = A/G, H = A/C/U) motif [166, 167]. Notably, Meyer's group [168] developed the deamination adjacent to RNA modification targets (DART-seq) method, which is an antibody-free approach for detecting m^{6}A sites. This method utilizes the apolipoprotein B mRNA editing catalytic subunit 1 (APOBEC1) fused with m^{6}A-binding YT521-B homology (YTH) domain to mediate the editing of cytosine to uracil (C to U) at sites adjacent to m^{6}A residues. However, it is limited by transfection efficiency [168].

In 2020, two novel approaches for detecting m^{6}A modifications were reported. One of them is the FTO-assisted m^{6}A selective chemical labeling method (m^{6}A-SEAL), which is a chemical labeling method that employs FTO as a catalyst to convert m^{6}A to hm^{6}A, followed by the conversion of unstable hm^{6}A to the sulfhydryl addition product dm^{6}A using dithiothreitol [169]. The labeled dm^{6}A is then captured for sequencing using streptavidin. While this method has good sensitivity and specificity, its resolution is not adequate [169]. On the other hand, m^{6}A-label-seq involves introducing Se-allyl-L-selenohomocysteine into cells, which gets labeled with allyl at the m^{6}A site, forming cyclized adenine under iodine induction [170]. RNA with cyclized adenine undergoes base mismatch during reverse transcription, thus enabling the identification of the location of m^{6}A modification on a single-base resolution basis. However, the labeling yield and time need further optimization [170].

In 2022, two novel m^{6}A RNA modification mapping methods for the entire transcriptome at single-base resolution were developed. The first method, called m^{6}A-selective allyl chemical labeling and sequencing (m^{6}A-SAC-seq), utilizes MjDim1 to add an allyl chemical group to m^{6}A to form a^{6}m^{6}A [171]. After a special chemical reaction, cyclization occurs, and the cyclized a^{6}m^{6}A is detected as a mutation by reverse transcriptase during reverse transcription. The position of m^{6}A in the transcriptome is then identified based on the mutation site, and accurate information about m^{6}A content is obtained by converting the standard curve through the mutation rate [171]. The second method is called glyoxal and nitrite-mediated deamination of unmethylated adenosines (GLORI), which can quantify m^{6}A with absolute stoichiometry at single-base resolution [172]. It is based on the principle of using glyoxal and nitrite to mediate the deamination of unmethylated adenosine without affecting the m^{6}A-modified adenosine, similar to bisulfite-sequencing-based quantification of DNA 5-methylcytosine [172].

Indeed, all of these methods offer a significant advancement in m^{6}A detection and mapping and can provide valuable insights into the regulation and function of m^{6}A in RNA modification. The next development of quantitative m^{6}A sequencing methods at the single-cell level is expected to open up new areas of research in RNA epigenetics.

7 | CONCLUSIONS AND PERSPECTIVES

Recently, the specific regulatory mechanisms of m^{6}A and its physiological functions have become a focus in the field of RNA research. With the in-depth studies of m^{6}A methylation, the diversity and complexity of its biological functions have gradually become more well-known, and many m^{6}A mechanisms in cancer have been elucidated, revealing that m^{6}A modifications and related regulatory proteins play vital roles in many cancers. Additionally, significant advancements have been made in m^{6}A editing techniques. One study found a site-specific m^{6}A writing and erasing tool that can edit RNA methylation without altering the nucleotide sequence or overall m^{6}A status. This tool acts as an m^{6}A "writer" to achieve specific m^{6}A modification of a single site in the 3' UTRs and 5' UTRs of mRNAs by fusing CRISPR-dCas9 with m^{6}A methyltransferases and can serve as an m^{6}A "eraser" by fusing CRISPR-dCas9 with ALKBH5 or FTO [173]. This innovative technology provides a powerful new scenery for investigating the relationship between m^{6}A methylation and cancer.

Interestingly, m^{6}A modification can also regulate gene transcription by affecting chromatin accessibility. Several recent reports have identified specific crosstalk between histone modification and RNA methylation. Huang et al. [174] discovered that H3K36me3 guides the dynamic deposition of m^{6}A modification via METTL14. Li et al. [175] uncovered a mechanism in which the m^{6}A reader YTHDC1 physically interacts with and recruits lysine demethylase 3B (KDM3B) to m^{6}A-associated chromatin

regions, promoting H3K9me2 demethylation and gene expression. Liu et al. [176] found that METTL3 deposits m^{6}A modifications on chromosome-associated regulatory RNAs (carRNAs) and decreases the levels of carRNAs, which suppresses chromatin accessibility and downstream transcription. Our recent work has demonstrated a regulatory mechanism of chromatin accessibility and gene transcription mediated by RNA m^{6}A formation coupled with DNA demethylation [177]. METTL3-mediated m^{6}A formation in RNA plays an important role in regulating DNA methylation and chromatin accessibility, which is mediated by the interaction between the m^{6}A reader fragile X mental retardation autosomal homolog 1 (FXR1) and the DNA 5-methylcytosine dioxygenase ten-eleven translocation 1 (TET1) [177, 178]. Recent studies have revealed that m^{6}A modification may regulate transcription by impacting histone modifications and DNA methylation, which provides new insights and research directions for studying the function and mode of m^{6}A modification. However, whether and how these epigenetic modifications interact with tumorigenesis and development remains to be investigated further.

While numerous studies have highlighted the significant roles of m^{6}A modification in tumorigenesis and development, translating these findings into clinical treatment for cancer requires further efforts. In order to develop more effective strategies for clinical cancer treatment, future research should prioritize fully elucidating the mechanisms and functions of m^{6}A in tumors.

DECLARATIONS

AUTHORS CONTRIBUTIONS

LXZ, XDH and JLZ designed and wrote the manuscript. DXL and JZ revised and supervised manuscript preparation. All authors read and approved the final manuscript.

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CONFLICT OF INTERESTS STATEMENT

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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