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Role of m⁶A RNA Methylation in Mediating Resistance to Chemotherapy and Immunotherapy in Cancer

Olli Johannes Laaksonen[1]*, Mikko Petteri Virtanen[1]

[1]Department of Oncology, University of Turku, Turku, Finland.

***E-mail** ✉ o.laaksonen@icloud.com

Abstract

The development of resistance to anticancer drugs is a major barrier to successful cancer therapy. Tumors that acquire such resistance often employ intricate molecular strategies to evade pharmacological treatment. Among epigenetic RNA modifications, N6-methyladenosine (m6A) is the most prevalent and reversible. Dysregulation of RNA methyltransferases ("writers"), demethylases ("erasers"), and m6A-binding proteins ("readers") has been observed in various malignancies, influencing oncoprotein levels and promoting tumor initiation, growth, progression, and metastasis. This review highlights the contribution of m6A modifications to therapy resistance. Changes in m6A patterns can alter drug responses by modulating multidrug efflux transporters, enzymes involved in drug metabolism, and direct drug targets. Additionally, m6A-mediated changes affect resistance through DNA repair pathways, adaptive responses (including apoptosis, autophagy, and oncogenic bypass signaling), cancer stem cell traits, tumor immune microenvironment dynamics, and exosomal non-coding RNAs. Notably, several small molecules that target m6A regulatory proteins have shown promising activity in overcoming drug resistance across different cancer types. Development of additional modulators of m6A-related proteins is anticipated to provide novel therapeutic approaches for tackling clinical drug resistance.

Keywords: Cancer drug resistance, m6A methylation, RNA modification, Chemotherapy, Immunotherapy

Introduction

Approximately 600,000 deaths worldwide each year are attributable to cancer, underscoring a persistent challenge for medical research [1, 2]. Current treatment strategies are primarily classified into five categories: surgical removal, chemotherapy, radiotherapy, immunotherapy, and targeted therapy [3, 4]. Although advancements have been achieved for specific cancer types, many therapies fail to produce the anticipated outcomes. A critical factor behind these failures is the incomplete understanding of molecular mechanisms driving therapeutic resistance. Chemotherapy resistance can be categorized as intrinsic or acquired [5]. Intrinsic (primary) resistance arises from preexisting genetic abnormalities, whereas acquired (secondary) resistance develops in response to treatment. Both forms are influenced by mutations and epigenetic alterations in cancer cell genomes. Drug efficacy is affected by multiple factors, including altered metabolism, transport systems, and modifications of target proteins [6]. Other key contributors include impaired apoptosis, enrichment of cancer stem cells (CSCs), dysregulation of oncogenes and tumor

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suppressors, and remodeling of the tumor immune microenvironment (TIME) [7, 8]. Yet, these are only part of the picture, and the exact mechanisms behind therapy-resistant cancers remain largely unresolved.

More than 160 distinct chemical modifications have been identified in RNA, opening the field of epitranscriptomics [9]. Among them, N6-methyladenosine (m6A) is one of the most abundant modifications found in eukaryotic mRNA [10, 11] and viral nuclear RNA [12, 13], initially reported in the 1970s. m6A modification is dynamic and reversible, controlled by methyltransferases ("writers") and demethylases ("erasers") **(Table 1)**. Known writers include METTL3 [14], METTL14 [15], WTAP [16], KIAA1429 [17], METTL16 [18], RBM15 [19], and ZC3H13 [20], whereas erasers include FTO [21] and ALKBH5 [22]. m6A-modified transcripts are recognized by reader proteins such as YTH domain-containing proteins [23], heterogeneous nuclear ribonucleoproteins (HNRNPs) that regulate splicing and RNA processing [24], insulin-like growth factor 2 mRNA-binding proteins (IGF2BP1/2/3) [25], and eIF3 [26].

Table 1. Functional roles of m6A in cancer biology

Type	m6A Regulator	Activity	Ref
m6A writer	METTL3	Catalyzes the methylation reaction	[14]
	METTL14	Assists METTL3 in recognizing the substrate	[15]
	METTL16	Catalyzes m6A modification	[18]
	WTAP	Promotes localization of the METTL3-METTL14 heterodimer into nuclear speckles	[16]
	KIAA1429	Directs methyltransferase components to specific RNA regions	[17]
	VIRMA	Recruits the methyltransferase core components and associates with polyadenylation cleavage factors CPSF5 and CPSF6	[27]
	RBM15	Binds the m6A complex and recruits it to specific RNA sites	[19]
	ZC3H13	Bridges WTAP to the mRNA-binding factor Nito	[20]
m6A eraser	FTO	Reduces methylated bases	[21]
	ALKBH5	Downregulates m6A modification levels	[22]
m6A reader	YTHDC1	Accelerates mRNA nuclear export and alternative splicing	[28]
	YTHDC2	Promotes translation of target RNAs	[29]
	YTHDF1	Enhances translation of mRNA	[30]
	YTHDF2	Accelerates mRNA degradation	[31]
	YTHDF3	Cooperates in mediating translation or degradation	[32]
	HNRNPA2B1	Promotes primary microRNA processing and alternative splicing	[24]
	HNRNPC	Influences mRNA splicing and maturation	[33]
	IGF2BP1/2/3	Enhance mRNA stability	[25]
	eIF3	Promotes cap-independent mRNA translation	[26]

Recent studies suggest that m6A modifications are strongly linked to therapeutic resistance. In many tumors, dysregulation of m6A regulators (writers, erasers, readers) controls oncoprotein levels and facilitates tumorigenesis and cellular proliferation [34]. m6A plays a role in several resistance mechanisms, including drug metabolism, transport, receptor targeting, stemness, DNA damage repair, and cell death [35–38]. Moreover, m6A influences immune responses within the tumor microenvironment, presenting new opportunities for immunotherapeutic strategies [39]. Small-molecule activators and inhibitors of m6A regulators have demonstrated potent anticancer effects, both as standalone agents and in combination with other therapies, highlighting m6A's potential in overcoming drug resistance [40]. This review focuses on the critical contribution of m6A to tumor drug resistance, explains mechanisms linking m6A modifications to therapy resistance, and discusses strategies targeting m6A to predict and manage resistant cancers **(Figure 1).**

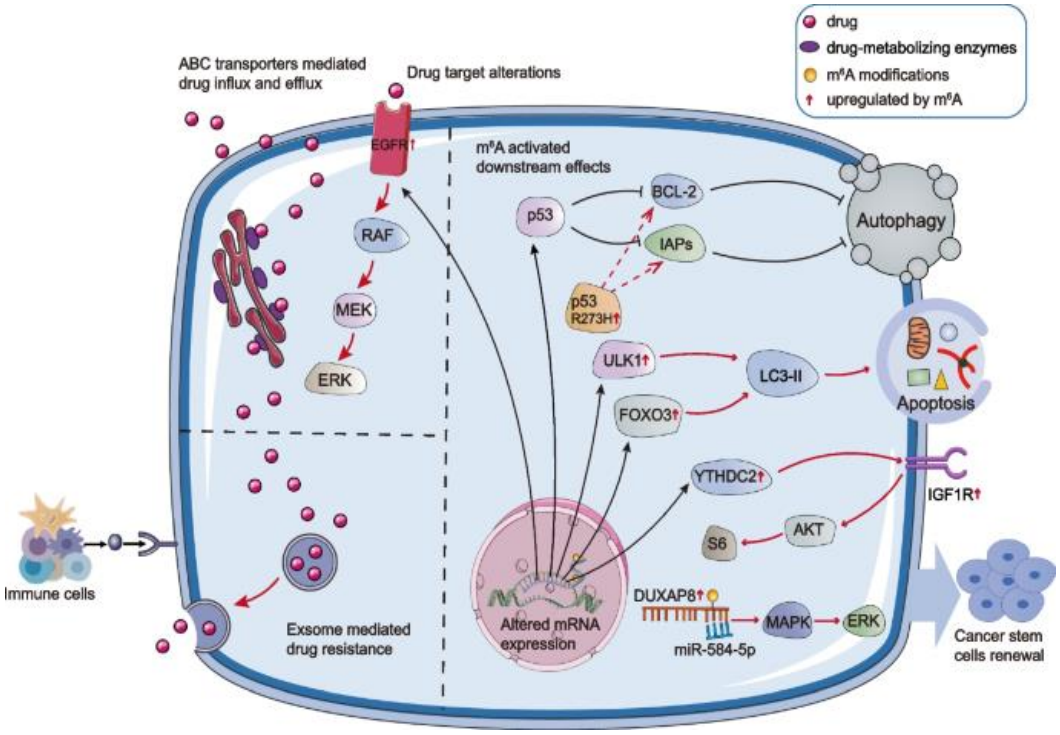

Figure 1. m6A-mediated mechanisms contributing to drug resistance**.**

m6A modifications influence multiple aspects of drug pharmacokinetics. By upregulating drug transporter proteins (e.g., ABCB1, ABCC1, ABCC10), m6A promotes ATP-dependent drug efflux. Additionally, m6A modulates drug-metabolizing enzymes (e.g., CYP2C8, UGT2B7), thereby affecting the therapeutic activity of chemotherapeutic agents. Certain drug targets, such as EGFR, are also regulated by m6A, influencing tumor progression. Beyond these effects, m6A participates in downstream pathways in three primary ways. First, it selectively increases mutant p53 (R273H), releasing suppressed anti-apoptotic proteins (e.g., BCL-2, IAPs). Second, it modulates key autophagy regulators (e.g., ULK1, FOXO3), ultimately controlling autophagy through LC3-II. Third, m6A triggers oncogenic bypass signaling via molecules like IGF1R and DUXAP8, promoting stem-like properties in cancer cells, a key contributor to drug resistance. Furthermore, m6A affects immune cell infiltration and cytokine production within the tumor microenvironment, relevant for immunotherapy. m6A modifications in exosomal non-coding RNAs also participate in multiple tumor-related biological processes and contribute to resistance against various anticancer drugs.

Mechanisms of m6A-mediated drug resistance

Resistance in cancer arises from multiple factors, including inter-individual differences in drug sensitivity, tumor site and type, aggressiveness, and intracellular molecular changes [3, 41]. m6A-mediated drug resistance involves effects on drug pharmacokinetics, tumor cell biology, and the tumor microenvironment. Understanding how m6A modifications regulate these mechanisms provides opportunities for personalized therapeutic strategies.

m6A in drug pharmacokinetics

m6A influences drug transport and metabolism

Membrane transporters play a critical role in drug efflux and chemotherapy resistance, with most studies focusing on ATP-binding cassette (ABC) proteins [42]. Multidrug resistance (MDR) is mediated by ABC transporters such as ABCB1 (MDR1), ABCC1 (MRP1), ABCC10 (MRP7), among others [43, 44]. Recent evidence indicates that m6A modifications regulate ABC transporter expression, either directly by acting on transcripts or indirectly through upstream signaling. For example, in chemo-resistant cells, m6A upregulates estrogen-related receptor gamma (ERRγ), which enhances ABCB1 transcription both directly and via increased interaction with p65 [45]. METTL3-mediated m6A also promotes ABCD1 translation, facilitating

migration and spheroid formation in clear cell renal cell carcinoma (ccRCC) [46]. Moreover, exosomal FTO enhances ABCC10 expression in recipient cells via the FTO/YTHDF2/ABCC10 axis, contributing to gefitinib resistance in non-small cell lung cancer (NSCLC) [47].

Besides transport, drug metabolism—including bioactivation, catabolism, conjugation, and elimination—affects chemotherapeutic efficacy [48]. m6A modifications negatively regulate several drug-metabolizing enzymes. METTL3/14 depletion increases CYP2C8 expression, whereas FTO depletion reduces it. Mechanistically, YTHDC2 recognizes m6A on CYP2C8 mRNA and promotes its degradation [49]. A similar negative regulation is observed for carboxylesterase 2 (CES2) [50]. UDP-glucuronosyltransferases (UGTs), which mediate glucuronidation, are also suppressed by m6A; for instance, UGT2B7 methylation in Huh-7 cells shows a negative correlation with m6A regulators [51]. Overall, m6A modifications act as novel regulators of both drug transport and metabolism, advancing personalized medicine.

m6A drives alterations in drug targets

Changes in drug targets, such as mutations or differential expression, influence drug responsiveness and resistance [52]. For instance, TP53 mutations (encoding p53) promote tumor progression and drug resistance. METTL3-mediated m6A induces the p53 R273H mutant, causing multidrug resistance in colon cancer cells **(Figure 1)** [53]. EGFR is another key therapeutic target; its activation enhances proliferation, inhibits apoptosis, and promotes angiogenesis and metastasis [54]. METTL3 increases EGFR translation, leading to RAF/MEK/ERK reactivation and acquired PLX4032 resistance in melanoma (**Figure 1**) [55]. Additionally, YTHDF1 and YTHDF2 bind m6A sites in the 3′-UTR of EGFR transcripts, contributing to dysregulated downstream signaling [56, 57]. Thus, m6A-mediated changes in p53 and EGFR impact drug efficacy and may guide strategies to reverse resistance.

m6A regulation in tumor cells

m6A and DNA damage repair

Many chemotherapeutic agents target DNA, causing lesions that inhibit transcription and replication [58]. METTL3 promotes oxaliplatin resistance in gastric cancer (GC) stem cells by enhancing DNA repair [59]. METTL3 also upregulates UBE2B, a key DNA repair enzyme, promoting multidrug resistance [60–62]. Other m6A regulators, including YTHDF1 and ALKBH5, contribute to resistance against adriamycin, cisplatin, and olaparib in breast cancer by facilitating DNA repair [63, 64].

m6A-triggered downstream effects

Anticancer agents typically exert their effects by engaging specific cellular targets to induce tumor cell death. m6A modifications influence a variety of downstream processes, including suppression of apoptosis, modulation of autophagy, and activation of oncogenic bypass pathways, which collectively contribute to therapeutic outcomes in cancer treatment [65, 66].

m6A in apoptosis regulation

The sensitivity of tumor cells to chemotherapeutic drugs is largely dictated by the expression of anti-apoptotic proteins, such as BCL-2, IAPs, and FLIP [67, 68]. Interestingly, m6A modifications can exert context-dependent effects on BCL-2 levels. For instance, elevated FTO expression correlates with increased BCL-2, a pattern similarly observed with ALKBH5 in epithelial ovarian cancer (EOC) [69, 70]. Thus, in some cancers, m6A is inversely related to anti-apoptotic activity. Conversely, other studies indicate a positive regulatory role: METTL3 depletion significantly enhanced apoptosis in breast cancer (BC) by reducing BCL-2 expression [71]. Likewise, in esophageal cancer, non-small cell lung cancer (NSCLC), and gastric cancer (GC), reduced m6A levels were associated with decreased BCL-2, promoting apoptosis [72–74]. Overall, m6A exhibits a dual function in regulating cell death, depending on tumor type.

m6A in autophagy regulation

Autophagy is a lysosome-dependent process that enables cells to cope with stress by degrading damaged organelles and proteins, often contributing to drug resistance [75–78]. m6A modifications can act as either suppressors or promoters of autophagy. In some cases, m6A inhibits autophagy **(Figure 2a).** For example, LC3B serves as a cytoplasmic marker of autophagy [79]. In hepatocellular carcinoma (HCC), METTL3 depletion increased LC3-II accumulation by destabilizing FOXO3 mRNA via a YTHDF1-dependent mechanism [80]. Similarly, FTO stabilizes ULK1 transcripts through YTHDF2, enhancing LC3-II accumulation [81]. FTO also promotes the translation of ATG5 and ATG7, further

facilitating autophagosome formation [82]. Conversely, m6A can stimulate autophagy in specific contexts (**Figure**. **2b**). In EOC, ALKBH5 stabilizes BCL-2 mRNA and activates the EGFR-PIK3CA-AKT-mTOR pathway to suppress autophagy [70]. Additionally, YTHDF3 enhances autophagy by recognizing METTL3-mediated m6A sites on FOXO3 mRNA [83], demonstrating the dual regulatory potential of m6A.

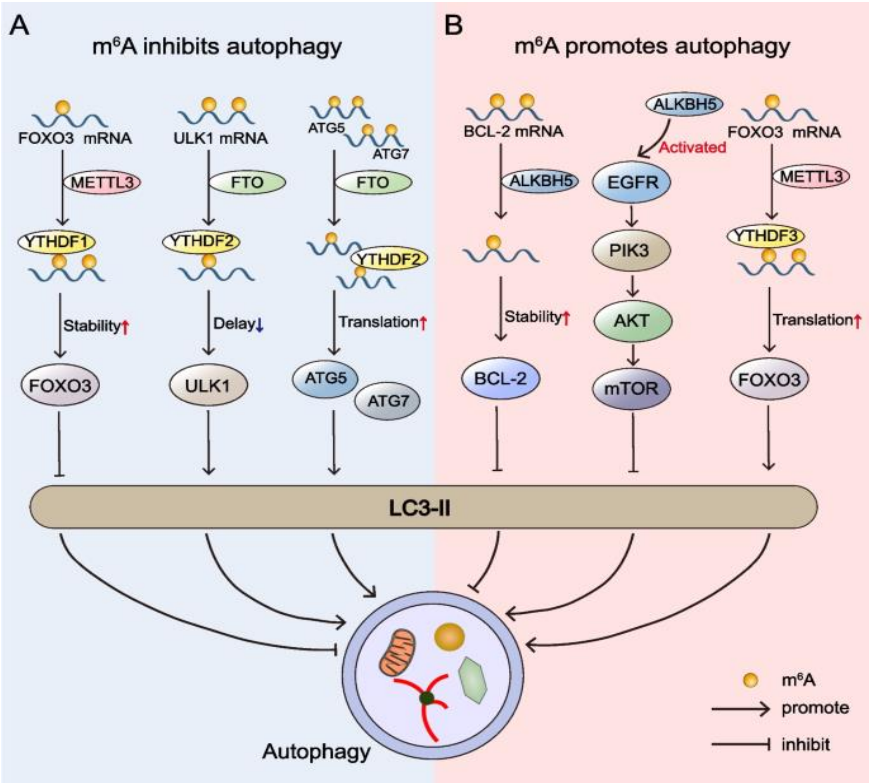

Figure 2. Dual roles of m6A in autophagy**.**

m6A modifications can either suppress or promote autophagy. In HCC, METTL3 stabilizes FOXO3 mRNA through YTHDF1, inhibiting LC3-II accumulation. FTO overexpression stabilizes ULK1 mRNA via YTHDF2 and promotes LC3-II accumulation, enhancing autophagosome assembly. Conversely, in EOC, ALKBH5 stabilizes BCL-2 mRNA and activates EGFR-PIK3CA-AKT-mTOR signaling to inhibit autophagy. YTHDF3 further promotes autophagy by upregulating FOXO3 translation.

m6A in oncogenic bypass signaling

Even with targeted therapies, tumors often acquire resistance due to activation of bypass signaling pathways, including Wnt/β-catenin, PI3K/AKT, MAPK, or c-MET cascades [84–86]. ALKBH5 reduces m6A levels on WIF-1 mRNA, promoting its transcription and potentially interfering with Wnt signaling to increase chemosensitivity [87]. Xu *et al*. [88] showed that m6A-modified circRNA-SORE is stabilized, sequestering miR-103a-2-5p and miR-660-3p and activating the Wnt/β-catenin pathway, resulting in sorafenib resistance. YTHDC2 regulates radiotherapy response via the IGF1R-AKT/S6 pathway, contributing to nasopharyngeal carcinoma resistance **(Figure 1)** [89]. Similarly, DUXAP8 modulates HCC malignancy and chemoresistance through the miR-584-5p/MAPK1/ERK axis **(Figure 1)** [90]. Chidamide lowers c-MET mRNA methylation, enhancing crizotinib sensitivity in NSCLC through a c-MET/HGF-dependent mechanism [91]. NKAP, an m6A reader, promotes SLC7A11 mRNA splicing and maturation, increasing resistance to ferroptosis inducers [92]. Collectively, m6A modifications activate oncogenic bypass pathways, bypassing classical drug targets, which is crucial for designing strategies to overcome therapy resistance **(Figure 3).**

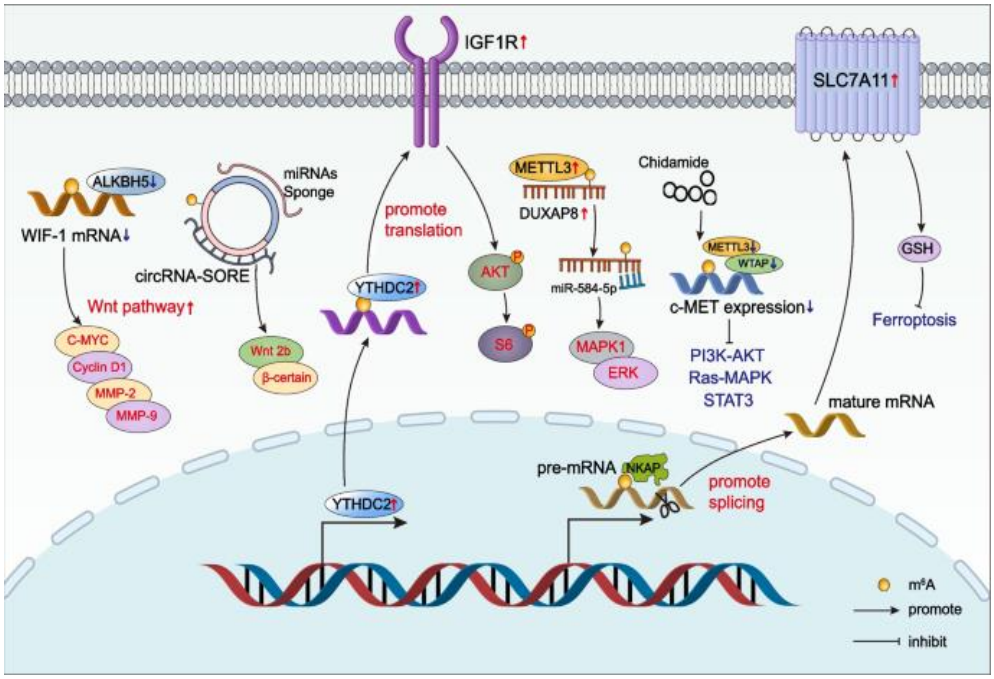

Figure 3. m6A-mediated regulation of oncogenic bypass pathways

Reduced ALKBH5 expression decreases WIF-1 mRNA levels, resulting in activation of the Wnt signaling pathway. Elevated m6A on circRNA-SORE increases its stability, enabling competitive activation of Wnt/β-catenin signaling by functioning as a miRNA sponge. YTHDC2 promotes resistance to radiotherapy through the IGF1R-AKT/S6 signaling cascade. m6A-modified DUXAP8 contributes to chemoresistance via the miR-584-5p/MAPK1/ERK axis. Chidamide reduces c-MET expression by decreasing m6A methylation, thereby enhancing crizotinib sensitivity. NKAP promotes SLC7A11 mRNA splicing and maturation, protecting cells from ferroptosis.

m6A and maintenance of cancer stemness

Cancer stem cells (CSCs), a small subset of tumor cells, maintain self-renewal capacity and drive tumor progression and drug resistance [93, 94]. METTL3 enhances stemness and influences chemosensitivity in colon cancer by upregulating LGR5 [95]. It also contributes to oxaliplatin resistance in CD133+ stem cells through stabilization of PARP1 mRNA and increased activity of the base excision repair pathway [59]. Liu *et al*. [96] identified a METTL14–miR-99a-5p–TRIB2 feedback loop promoting CSC properties and radioresistance in esophageal squamous cell carcinoma (ESCC). m6A modification of circHPS5 facilitates cytoplasmic export and supports epithelial-to-mesenchymal transition (EMT) and CSC traits, accelerating hepatocellular carcinoma (HCC) tumorigenesis [97]. HNRNPA2B1 promotes the CD44+/CD24−/low CSC population and modifies EMT markers, driving acquired endocrine resistance via activation of serine/threonine kinase growth factor signaling [98]. Although research linking m6A to CSC biology is still limited, targeting m6A in CSCs may represent a promising avenue for overcoming drug resistance.

m6A in the tumor immune microenvironment

m6A regulates TIME features

Emerging evidence shows that m6A modifications shape the tumor immune microenvironment (TIME), highlighting m6A regulators as potential immunotherapy targets [99]. METTL3 exhibits dual effects on immune cell infiltration: in testicular germ cell tumors, METTL3 downregulation correlates with increased infiltration of CD8+ T cells, CD4+ T cells, and NK cells [100]. Conversely, depletion of METTL3 or METTL14 enhances cytotoxic CD8+ T cell infiltration and elevates IFN-γ, CXCL9, and CXCL10 levels, improving responsiveness to anti-PD-1 therapy in pMMR-MSI-L colorectal cancer (CRC) [101]. Overexpression of

WTAP in gastric cancer (GC) negatively impacts T cell infiltration and T cell-mediated immunity, correlating with poor prognosis [102]. FTO depletion reprograms immune responses, enhancing T cell cytotoxicity by downregulating immune checkpoint genes, including LILRB4 [103]. In melanoma, combining FTO inhibition with PD-1/PD-L1 blockade alleviates immunotherapy resistance [104]. FTO also modulates glycolytic metabolism and suppresses CD8+ T cell function [105]. ALKBH5 expression correlates with Treg infiltration; its deletion improves anti-PD-1 therapy outcomes in melanoma [106]. Recent studies demonstrate that m6A readers YTHDF1 and YTHDF2 positively associate with immune checkpoint receptor expression (PD-1, TIM-3, CTLA-4) and lymphocyte infiltration (B cells, T cells, macrophages, dendritic cells) across multiple cancers, including glioma, NSCLC, kidney renal clear cell carcinoma, and breast cancer [107–110]. Despite TIME variability among tumor types and individuals, correcting m6A dysregulation presents a viable immunotherapeutic strategy **(Figure 4).**

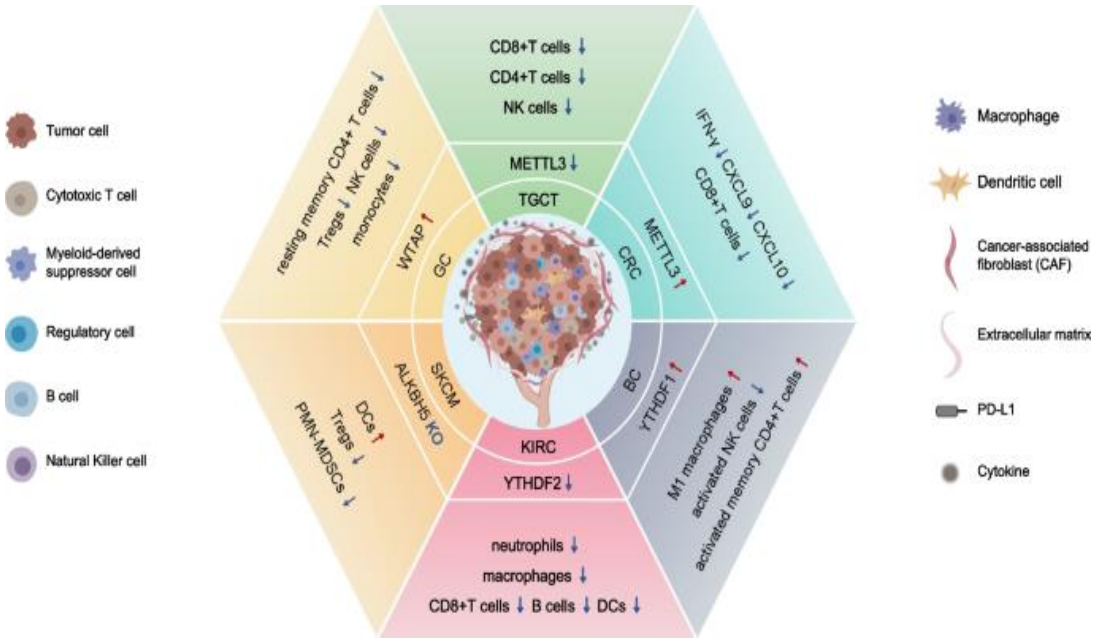

Figure 4. m6A-mediated modulation of the tumor immune microenvironment.

In testicular germ cell tumors, METTL3 downregulation positively correlates with infiltration by CD8+ T cells, CD4+ T cells, and NK cells. WTAP overexpression in granulosa cells (GCs) is negatively associated with T cell infiltration and function. In skin cutaneous melanoma (SKCM), ALKBH5 knockout reduces Treg and PMN-MDSC infiltration while increasing dendritic cell presence. In kidney renal clear cell carcinoma (KIRC), YTHDF2 downregulation correlates with increased lymphocyte infiltration (B cells, T cells, macrophages, neutrophils, dendritic cells). In breast cancer (BC), high YTHDF1 expression associates with elevated infiltration of activated memory CD4+ T cells and M1 macrophages, but lower NK cell infiltration. In mismatch-repair-proficient or microsatellite instability-low CRC, METTL3 overexpression decreases IFN-γ, CXCL9, and CXCL10 secretion in the TIME.

m6A modifications in exosomal non-coding RNAs

Exosomes are nanoscale extracellular vesicles containing components from their parental cells, playing a vital role in tumor-stroma communication and mediating therapy resistance [111, 112]. The impact of exosomal non-coding RNAs on drug resistance has only recently been explored. Liu *et al*. [113] reported that METTL3 enhances the maturation of pri-miR-320b, which is linked to peritumoral lymphangiogenesis and lymph node metastasis. Additionally, METTL3 promotes the exosomal transfer of miR-181b-5p from cancer-associated fibroblasts (CAFs), reducing colorectal cancer (CRC) cell sensitivity to 5-fluorouracil (5-FU) via the METTL3/miR-181d-5p axis [114]. In non-small cell lung cancer (NSCLC), cisplatin-resistant exosomes showed significantly elevated miR-4443, which

suppresses FSP1-mediated ferroptosis induced by cisplatin in vitro and enhances tumor growth in vivo through METTL3-dependent m6A modification [115]. Exosome-mediated circVMP1 also contributes to cisplatin resistance through the miR-524-5p-METTL3/SOX2 axis [116]. Furthermore, exosomal long non-coding RNAs (lncRNAs) serve as regulators of drug resistance; for example, adipocyte-derived exosomes carrying lncRNAs from multiple myeloma (MM) cells via METTL7A-mediated methylation lead to therapeutic resistance [117].

m6A-driven specific drug resistance

Recent studies indicate that m6A RNA methylation contributes to resistance against various chemotherapeutic agents by modulating different targets or pathways. In lung adenocarcinoma (LUAD), METTL7B overexpression increases m6A levels, driving resistance to gefitinib and osimertinib through a ROS-scavenging-dependent mechanism [118]. YTHDF2-mediated endoribonucleolytic cleavage of m6A-modified circASK1 also promotes gefitinib resistance in LUAD [119]. ALKBH5 demethylates m6A on CASC8, stabilizing its transcription and causing cisplatin resistance in esophageal squamous cell carcinoma (ESCC) [120]. Similarly, YTHDF2 accelerates CDKN1B mRNA degradation in an m6A-dependent manner, fostering intrahepatic cholangiocarcinoma (ICC) progression and diminishing cisplatin sensitivity [121].

m6A modifications also contribute to tamoxifen resistance in breast cancer (BC). METTL3 enhances AK4 mRNA translation by increasing m6A, elevating ROS production, and activating p38, ultimately driving tamoxifen resistance [122]. HNRNPA2B1, an m6A reader, also mediates tamoxifen resistance through downstream activation of serine/threonine kinase growth factor signaling [98]. In glioblastoma multiforme (GBM), METTL3 increases m6A on transcripts of histone-modifying genes, resulting in temozolomide resistance [123]. In clear cell renal cell carcinoma (ccRCC), YTHDC1 regulates sensitivity to tyrosine kinase inhibitors, including sunitinib, via the YTHDC1/ANXA1 axis [124]. Overall, these findings highlight the central role of m6A in mediating chemotherapy resistance, providing potential avenues for targeted interventions **(Figure 5).**

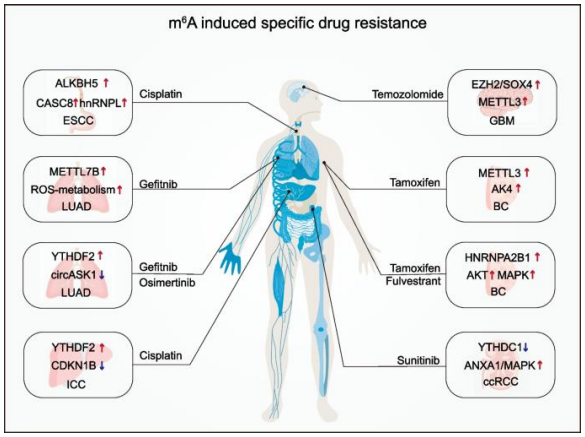

Figure 5. m6A-mediated specific chemoresistance**.**

Resistance to chemotherapy in ESCC, LUAD, ICC, GBM, BC, and ccRCC is associated with m6A modifications and their regulatory proteins.

Targeting m6A to overcome drug resistance

As discussed, m6A modifications have dual roles in driving resistance, but their underlying molecular mechanisms remain incompletely understood. Beyond m6A site mutations, each tumor exhibits distinct functions of m6A regulators [125], highlighting the importance of targeting m6A machinery in cancer therapy **(Table 2).**

Table 2. Role and mechanisms of m6A regulators in cancer drug resistance

m6A regulator	Cancer type	Role in cancer	Expression in cancer drug resistance	Drug	Target genes	Mechanism	Ref
METTL3	BC	Oncogene	High	Adriamycin	MALAT1	METTL3 increased MALAT1 protein levels and triggered the MALAT1/E2F1/AGR2 pathway	[126]
METTL3	NSCLC	Oncogene	NA	Cisplatin	YAP	METTL3 boosted YAP mRNA translation via	[127]

						recruitment of YTHDF1/3 and eIF3b	
METTL3	HCC	Oncogene	Low	Sorafenib	FOXO3	METTL3 enhanced FOXO3 protein stability in a YTHDF1-dependent manner	[80]
METTL3	HCC	Oncogene	High	Adriamycin	ERRγ	METTL3 extended the half-life of ERRγ precursor mRNA	[45]
METTL3	CRC	Oncogene	NA	Oxaliplatin or irinotecan	CBX8	METTL3 stabilized CBX8 mRNA in an IGF2BP1-dependent fashion	[95]
METTL3/14	CRC	NA	NA	anti-PD-1 antibodies	STAT1 and IRF1	Loss of METTL3 or METTL14 enhanced IFN-γ-Stat1-Irf1 signaling by stabilizing Stat1 and Irf1 mRNA through YTHDF2	[101]
METTL3,WTAP	NSCLC	Oncogene	NA	Crizotinib	c-MET	Reduced expression of METTL3 and WTAP led to lower c-MET levels	[91]
WTAP	BLCA	Oncogene	High	Cisplatin	TNFAIP3	Circ0008399 interacted with WTAP to activate the circ0008399/WTAP/TNFAIP3 axis	[128]
WTAP	NKTCL	Oncogene	High	Cisplatin	DUSP6	WTAP upregulated DUSP6 expression	[129]
WTAP	BC	Oncogene	High	Adriamycin	DLGAP1-AS1	WTAP increased the stability of DLGAP1-AS1	[130]
FTO	GBM	Oncogene	NA	Temozolomide	PDK1	JPX bound to FTO, resulting in reduced PDK1 expression	[131]
FTO	MM	Oncogene	High	Bortezomib	SOD2	FTO reduced SOD2 expression	[132]
FTO	BC	Oncogene	High	Doxorubicin	STAT3	FTO activated STAT3 signaling pathway in breast cancer cells	[133]
FTO	CSCC	Oncogene	High	Cisplatin	β-Catenin	FTO increased β-catenin gene expression through m6A demethylation	[134]
FTO	Leukemia	Oncogene	High	Imatinib, nilotinib, or PKC412	MERTK and BCL-2	FTO-mediated m6A demethylation enhanced the stability of MERTK and BCL-2	[69]
ALKBH5	PC	Tumor suppressor	Low	Gemcitabine	WIF-1	ALKBH5 boosted WIF-1 transcription, thereby inhibiting Wnt pathway	[87]
ALKBH5	EOC	Oncogene	High	Cisplatin	JAK2	The ALKBH5-HOXA10 positive feedback loop activated JAK2/STAT3 signaling	[135]
ALKBH5	T-ALL	Oncogene	High	Glucocorticoid	USP1	ALKBH5 elevated expression of USP1 and Aurora B	[136]
ALKBH5	EOC	Oncogene	Low	Olaparib	FZD10	Reduced levels of FTO and ALKBH5 led to increased FZD10 mRNA	[137]

ALKBH5	OSCC	Oncogene	High	Cisplatin	FOXM1	ALKBH5 upregulated FOXM1 by demethylating its nascent transcripts	[138]
YTHDF1	NSCLC	Oncogene	Low	Cisplatin	Keap1	YTHDF1 increased Keap1 mRNA translation efficiency	[139]
IGF2BP3	CRC	NA	High	Doxorubicin	ABCB1	IGF2BP3 stabilized and enhanced expression of ABCB1 mRNA	[140]
HNRNPC	GC	Oncogene	High	5-FU, paclitaxel, or cisplatin	NA	Monoclonal antibody 5B2 targeted overexpressed HNRNPC in chemotherapy-resistant gastric cancer cells	[30]

METTL3

As a key m6A "writer," METTL3 plays a central role in cancer initiation and progression across multiple malignancies, including glioblastoma, breast cancer (BC), hepatocellular carcinoma (HCC), leukemia, and others [141–144]. Suppression of METTL3 can reverse tumor resistance to chemotherapy or radiotherapy, although its functional effects may be tissue- or lineage-specific. A recent study demonstrated that elevated METTL3 expression stabilizes SOX2 mRNA, and its knockdown enhances glioblastoma stem cells' (GSCs) sensitivity to γ-H2AX and efficient DNA repair, thereby restoring radiosensitivity [145]. Additionally, METTL3 silencing improves temozolomide response, inhibits proliferation, and induces apoptosis. Taketo *et al*. [62] reported that inhibition of METTL3 increased tumor cell susceptibility to chemotherapy and radiotherapy, linking METTL3 to alternative regulation of MAPK signaling, particularly in patients treated with gemcitabine, 5-FU, and cisplatin.

Uddin and colleagues [53] revealed that METTL3 preferentially catalyzes pre-mRNA splicing at TP53 codon 273 (G>A), resulting in enhanced translation of mutant p53 protein and subsequent multidrug resistance (MDR). METTL3 also recruits m6A to the translation initiation complex, directly promoting yes-associated protein (YAP) synthesis. Moreover, METTL3 in complex with YTHDF3 stabilizes MALAT1, which subsequently drives YAP expression via the MALAT1–miR-1914-3p–YAP axis, contributing to cisplatin (DDP) resistance and metastasis [127].

Beyond DDP, METTL3-mediated m6A promotes resistance to other chemotherapeutic agents in NSCLC. For instance, chidamide decreases c-MET mRNA methylation, enhancing crizotinib sensitivity in a c-MET/HGF-dependent manner [91]. In HCC under hypoxia, METTL3 depletion, which destabilizes FOXO3 mRNA, reduces sorafenib resistance, identifying FOXO3 as a critical downstream target of m6A in sorafenib-resistant HCC [80]. METTL3 also participates in adriamycin (ADR) resistance in BC: m6A-dependent regulation of MALAT1 recruits E2F1 and induces AGR2 expression, promoting ADR resistance [126]. Furthermore, in gastric cancer (GC), IGF2BP1 recognizes METTL3-mediated m6A on apoptotic protease-activating factor 1-binding lncRNA, stabilizing it and thereby inhibiting apoptosis and promoting multidrug resistance [146]. Importantly, m6A-targeted transcription factors vary between cancer types, and further research is needed to clarify METTL3's regulatory mechanisms to optimize therapeutic targeting.

WTAP

WTAP is another crucial component of the m6A methyltransferase complex, interacting with METTL3 and METTL14 to catalyze m6A deposition on pre-mRNAs and hnRNAs. Knockdown of WTAP markedly reduces m6A levels and induces apoptosis [16]. Bansal *et al.* [147] proposed that WTAP overexpression has oncogenic effects in leukemogenesis, correlating with poor prognosis in acute myeloid leukemia (AML). WTAP may act as an HSP90 client protein, maintaining the stability of oncoproteins and limiting etoposide efficacy. Silencing WTAP in K562 cells significantly increased apoptosis in response to etoposide, suggesting that combining WTAP inhibition with etoposide could enhance AML cell death.

In bladder cancer (BLCA), circ0008399, a circular RNA, stabilizes TNFAIP3 mRNA in an m6A-dependent manner, with WTAP reducing CDDP sensitivity via the circ0008399/WTAP/TNFAIP3 axis [128]. Ma *et al.* [129] reported that WTAP-mediated upregulation of DUSP6 contributes to carcinogenesis and drug resistance in nasal-type natural killer/T-cell lymphoma (NKTCL),

providing a basis for novel therapeutic strategies. Similarly, WTAP binding to m6A-modified DLGAP1-AS1 enhances its stability, promoting ADR resistance in BC through the WTAP/DLGAP1-AS1/miR-299-3p feedback loop [130].

Targeting demethylases

FTO

The m6A demethylase FTO functions as an oncogene in breast cancer (BC), acute myeloid leukemia (AML), and other malignancies [148–150]. FTO-mediated m6A alterations are also implicated in chemoresistance in multiple cancers, including multiple myeloma (MM), glioblastoma, and melanoma. Yan *et al.* [69] demonstrated that TKI tolerance in leukemia patients arose from FTO overexpression, which reduced m6A levels. Constitutive activation of signal transducer and activator of transcription 3 (STAT3) occurs in several cancer types and correlates with poor prognosis [151]. Wang *et al*. [133] observed that doxorubicin-resistant BC cells had elevated FTO and STAT3, with STAT3 binding to the FTO promoter to enhance its expression. FTO also mediated STAT3-dependent doxorubicin resistance, reducing drug sensitivity in BC cells. In cervical squamous cell carcinoma (CSCC), FTO overexpression induced radiotherapy and chemotherapy resistance via mRNA demethylation and ERCC1 regulation [134].

In MM patients, high FTO levels were detected in bone marrow cells, and FTO promoted bortezomib resistance by destabilizing SOD2 in an m6A-dependent manner, suggesting potential therapeutic strategies [132]. Additionally, the lncRNA JPX interacts with FTO and PDK1 mRNA, enhancing its stability and demethylation, thus promoting glioblastoma temozolomide resistance via the FTO/PDK1 axis [131]. Knockdown of FTO reduces the stability of PD-1, CXCR4, and SOX10 through YTHDF2-mediated m6A-dependent RNA decay, increasing sensitivity to IFN-γ and anti-PD-1 therapy in melanoma cells.

ALKBH5

ALKBH5, another m6A demethylase, is involved in tumorigenesis and progression in colon cancer, bladder cancer (BLCA), epithelial ovarian cancer (EOC), and oral squamous cell carcinoma (OSCC) [152–154]. In BRCA2-mutated ovarian cancers, downregulation of FTO and ALKBH5 enhanced FZD10 m6A methylation, reducing PARPi sensitivity via the Wnt/β-catenin pathway [137]. ALKBH5 also drives cisplatin resistance: the transcription factor HOXA10 forms a regulatory loop with ALKBH5, activating JAK2/STAT3 signaling and promoting EOC cisplatin resistance through JAK2 m6A demethylation [135].

ALKBH5 promotes chemoresistance in other cancers as well. In T-cell acute lymphoblastic leukemia (T-ALL), ALKBH5 stabilizes USP mRNA, contributing to tumor growth and drug resistance [136]. The RNA helicase DDX3 directly regulates ALKBH5 to reduce m6A on FOXM1 and NANOG transcripts, conferring cisplatin resistance in OSCC [138]. Depletion of ALKBH5 sensitizes tumors to immunotherapy, indicating its potential as a therapeutic target in melanomas, colorectal cancer (CRC), and other malignancies [106]. In pancreatic cancer (PC), ALKBH5-mediated m6A promotes DDIT4-AS1 overexpression, which enhances cancer stemness and gemcitabine resistance via DDIT4 destabilization and mTOR pathway activation [155].

Targeting other m6A regulators

While most m6A-targeted strategies focus on methyltransferases like METTL3 and WTAP or demethylases, evidence suggests additional m6A modulators may be viable therapeutic targets. METTL14 depletion significantly slows tumor growth and extends survival in mouse models of CT26 CRC and B16 melanoma [101]. m6A reader proteins also contribute to chemoresistance: in NSCLC, YTHDF1 depletion leads to Keap1 degradation, activating the Keap1-Nrf2-AKR1C1 axis and promoting cisplatin resistance [139]. MicroRNA-145 can counteract YTHDF2's oncogenic role in HepG2 cells associated with HCC [156]. In CRC, hypoxia-induced lncRNA STEAP3-AS1 competes with YTHDF2 for binding to STEAP3 mRNA, preventing m6A-mediated degradation and elevating STEAP3 protein, which activates Wnt/β-catenin signaling and tumor progression [157].

Additionally, paclitaxel, 5-FU, and cisplatin are more effective in HNRNPC-deficient cell lines [33]. IGF2BP3, another m6A reader, binds the m6A region of ABCB1 mRNA, enhancing chemoresistance in CRC [140]. Collectively, these findings indicate that HNRNPC and IGF2BP3 may serve as potential biomarkers for chemoresistance.

m6A-targeted compounds

FTO inhibitors

Rhein was the first discovered FTO inhibitor functioning both in vitro and in vivo. Unlike 2OG mimics or metal

ion chelators, rhein competitively bound to FTO's catalytic site to block its demethylase activity [158]. In therapeutic applications, combining rhein with TKIs effectively eradicated relapsed/refractory leukemia [69], and rhein treatment increased m6A levels in leukemia cells. Notably, 24-hour exposure to 20 μM rhein did not induce growth arrest, suggesting its potential for anticancer therapy. Ascorbic acid and its analog MO-I-500 also enhanced 2OG-dependent dioxygenase activity, displaying antiproliferative effects in BC in an FTO-dependent manner [159,160]. However, both rhein and MO-I-500 act as broad-spectrum 2-OG inhibitors, limiting their applications.

Meclofenamic acid (MA), a non-steroidal anti-inflammatory drug identified via high-throughput fluorescence polarization assays, inhibited FTO. Its ethyl ester derivative, MA2, increased m6A levels in mRNA [161] and suppressed self-renewal and tumorigenesis of GSCs in xenograft models, extending survival [162]. MA2 also enhanced chemotherapy effects in glioma [163]. Based on MA's specificity, more potent derivatives were synthesized. FB23, an MA derivative, selectively inhibited FTO with 140-fold higher potency, while its practical analog FB23–2 exerted FTO-dependent anti-leukemia activity [164]. Another derivative, Dac51, inhibited FTO, remodeled the tumor microenvironment, and increased CD8+ T cell infiltration, improving antitumor efficacy [105]. FTO-04 strongly inhibited neurosphere formation in patient-derived GSCs without affecting normal human neural stem cells, elevating m6A and m6Am levels [165]. Nafamostat mesylate, traditionally used in pancreatitis, also inhibited FTO activity [166]. R-2-hydroxyglutarate (R-2HG), a 2OG analog, competitively blocked FTO, increasing m6A levels and suppressing aerobic glycolysis by targeting downstream molecules including MYC, CEBPA, PFKP, and LDHB [167, 168]. CS1 and CS2 demonstrated higher efficacy than previous inhibitors (FB23–2 and MO-I-500) in reducing AML cell viability [103]. Collectively, FTO inhibitors represent a promising therapeutic approach, though long-term safety remains to be evaluated.

METTL3 inhibitors

Bedi *et al*. [169] screened approximately 4000 adenosine derivatives to discover potential METTL3 inhibitors. The best candidate, a S-adenosyl-L-methionine (SAM) mimic, was the first small molecule reported to inhibit METTL3. These inhibitors exhibited strong ligand efficiency and binding modes validated by protein crystallography. For instance, STM2457 selectively reduced m6A levels on leukemogenic mRNAs, suppressing AML growth while promoting differentiation and apoptosis [170]. Another inhibitor, UZH1a, decreased the m6A/A ratio across various cell lines, highlighting the therapeutic potential of METTL3 inhibition in diverse disease models [171].

Other m6A regulator activators and inhibitors

In silico screening identified small molecules binding the METTL3–14-WTAP complex. SAM interacts with Asp377 and forms a hydrogen bond with Asp395 of METTL3, while four other compounds bind to Asp295, Phe534, Arg536, and Asn539 of METTL3, activating the METTL3-METTL14 complex to enhance mRNA m6A methylation [172]. However, further validation is required to confirm their anticancer effects.

Li *et al*. [106] used X-ray crystal structure-based screening to identify ALK-04, a specific ALKBH5 inhibitor. ALK-04 significantly reduced melanoma growth in mice and demonstrated potential for combination with immunotherapy. BTYNB, discovered via compound library screening, selectively inhibited c-Myc and IGF2BP1, destabilizing E2F1 mRNA and impeding tumor growth [173]. **Table 3** summarizes currently identified m6A-targeted compounds.

Table 3. Identified m6A-targeted compounds

Molecule	Target	Activity	IC50 (of target) (μM)	Mechanism in cancer/ cell line	Validated cancer type/ cell line type	Identified year	Ref
rhein	FTO, ALKBH2, ALKBH3	inhibit	21 (FTO)	rhein reversed nilotinib resistance through suppression of FTO activity	leukemia	2012	[69, 158]
MO-I-500	FTO	inhibit	8.7	MO-I-500 suppressed survival and colony formation in breast cancer cells	BC	2014	[159, 160]

MA2	FTO	inhibit	7	MA2 treatment suppressed growth and self-renewal of glioblastoma stem cells	GBM	2014	[161, 165]
FB23–2	FTO	inhibit	0.06	FB23–2 inhibited proliferation and induced differentiation and apoptosis in AML cells	AML	2019	[164]
Dac51	FTO	inhibit	0.4	Dac51 enhanced $CD8^+$ T cell infiltration and showed synergy with anti-PD-L1 therapy	SKCM, lung cancer	2021	[105]
FTO-04	FTO, ALKBH5	inhibit	3.39 (FTO)	prevented neurosphere formation in patient-derived glioblastoma stem cells	GBM	2021	[165]
R-2HG	FTO	inhibit	133.3	R-2HG suppressed cancer cell proliferation/survival via the FTO/m6A/MYC/CEBPA pathway	AML	2018	[167]
CS1	FTO	inhibit	0.143	CS1 and CS2 displayed anti-leukemic activity by promoting apoptosis and suppressing MYC pathways	AML	2020	[103]
CS2	FTO	inhibit	0.713		AML	2020	[103]
adenosine	METTL3	inhibit	500	NA	NA	2020	[169]
STM2457	METTL3	inhibit	0.0169	STM2457 inhibited AML growth while promoting differentiation and apoptosis	AML	2021	[170]
U2H1a	METTL3	inhibit	7	U2H1a decreased m6A levels in the mRNA fraction	AML, osteosarcoma, HEK293T	2021	[171]
ALK-04	ALKBH5	inhibit	NA	ALK-04 suppressed tumor growth and improved the effectiveness of anti-PD-1 treatment	melanoma, CRC	2019	[106]
BTYNB	IGF2BP1	inhibit	6	BTYNB reduced tumor cell proliferation and suppressed E2F-dependent gene expression	HepG2, A549, ES-2, PANC-1, MV3	2017	[174]
METTL3/14-WTAP compounds	METTL3	activate	0.281	The compounds elevated mRNA m6A levels and influenced cell cycle regulation	HEK293 cell	2019	[172]
MPCH	METTL3/14	activate	NA	MPCH stimulated METTL3/14 activity, leading to substantial m6A hypermethylation upon brief UV exposure	A549, MCF-7, HeLa	2021	[175]
IDH2	FTO	activate	NA	IDH2 increased FTO activity and promoted tumorigenesis and disease progression in multiple myeloma	MM	2021	[176]

Conclusion

Although substantial research has focused on elucidating the roles of m6A modifications in cancer growth and therapeutic resistance, numerous questions remain unresolved. For instance, as a widespread RNA modification in eukaryotic mRNAs, can compounds targeting m6A regulators serve as effective anticancer therapies? How can we selectively focus on critical molecular targets? And what strategies can specifically modulate the m6A regulatory axes to reverse drug resistance within tumor tissues?

The functional significance of m6A modifications and their regulators points toward a promising avenue for targeted therapy. Yet, only a limited number of inhibitors and activators associated with m6A phenotypes are clinically viable. Several factors may explain this gap. First, there is insufficient data on the cellular activity of these compounds, making their effects on methylation levels uncertain. Second, adenosine analogs often exhibit poor cell permeability and suboptimal pharmacokinetics, limiting their therapeutic potential. Third, tumor heterogeneity and the scarcity of reliable predictive biomarkers create obstacles for applying these targeted compounds across diverse cancer types. Consequently, additional screening for potent agents is necessary.

To achieve precise regulation of m6A modifications—whether globally or at specific sites—targeting protein-protein interactions (PPI) or protein-nucleotide interactions represents a promising strategy. Further investigations into tumor biology, development of high-quality chemical probes, and rigorous preclinical studies are essential to identify accurate biomarkers, which are critical for individualized therapy, outcome improvement, and toxicity prediction. Moreover, most currently reported m6A-targeting compounds are cytotoxic, whereas non-cytotoxic modulators that influence the immune system may provide valuable combinatory approaches. For example, the ALKBH5 inhibitor ALK-04 demonstrated substantial synergy with anti-PD-1 therapy in vivo without inducing cytotoxicity. Overall, the clinical implementation of m6A-targeted compounds remains in its early stages. As understanding of cancer epigenomics deepens, these therapies hold considerable potential for patients exhibiting therapy-resistant tumors driven by aberrant m6A modifications.

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