

REVIEW

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Writers, readers, and erasers RNA modifications and drug resistance in cancer

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Abstract

Drug resistance in cancer cells significantly diminishes treatment efficacy, leading to recurrence and metastasis. A critical factor contributing to this resistance is the epigenetic alteration of gene expression via RNA modifications, such as N6-methyladenosine (m6A), N1-methyladenosine (m1A), 5-methylcytosine (m5C), 7-methylguanosine (m7G), pseudouridine (Ψ), and adenosine-to-inosine (A-to-I) editing. These modifications are pivotal in regulating RNA splicing, translation, transport, degradation, and stability. Governed by “writers,” “readers,” and “erasers,” RNA modifications impact numerous biological processes and cancer progression, including cell proliferation, stemness, autophagy, invasion, and apoptosis. Aberrant RNA modifications can lead to drug resistance and adverse outcomes in various cancers. Thus, targeting RNA modification regulators offers a promising strategy for overcoming drug resistance and enhancing treatment efficacy. This review consolidates recent research on the role of prevalent RNA modifications in cancer drug resistance, with a focus on m6A, m1A, m5C, m7G, Ψ, and A-to-I editing. Additionally, it examines the regulatory mechanisms of RNA modifications linked to drug resistance in cancer and underscores the existing limitations in this field.

Keywords Epigenetic alterations, Drug resistance, Abnormal expression, Combination therapy, RNA modification regulators

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Introduction

Chemotherapy, targeted therapy, and immunotherapy serve as primary treatment strategies for cancer [1–5]. Nonetheless, patients with advanced cancer often show poor responses to these interventions [6–10]. Cancer cells circumvent these treatments' toxic effects through intrinsic resistance, stemming from pre-existing genetic and epigenetic variations, or acquired resistance, which emerges during therapy [11–17]. Principal mechanisms of therapeutic resistance include increased drug efflux, altered drug metabolism, and modified expression of therapeutic targets [8, 18–20]. Additionally, cancer cells can activate anti-apoptotic pathways, enhance DNA repair, initiate autophagy, remodel the tumor microenvironment (TME), and induce epithelial-mesenchymal transition (EMT), all contributing significantly to cancer cell survival and drug resistance [14, 21–24].

Beyond these factors, epigenetic regulation is pivotal in mediating drug resistance [25–29]. Epigenetic modifications, such as RNA modifications, influence gene expression without altering the DNA sequence [30–33]. With advancements in high-throughput detection methods, RNA methylation has been recognized for its critical role in global epigenetic remodeling [34–38]. RNA modifications occur on various types of RNAs and are essential for regulating RNA processing, including splicing, localization, transport, translation, and degradation [39–42]. These modifications alter the chemical and topological properties of the four basic nucleotides, thereby influencing the stability and function of the modified RNAs. Similar to DNA and proteins, RNAs undergo methylation and demethylation by specific enzymes known as methyltransferases (“writers”) and demethylases (“erasers”) [43–47]. Writers install RNA modifications by recognizing the sequence and structure of substrate RNAs, interacting with the transcriptional machinery or RNA-binding proteins (RBPs), while demethylases reverse these modifications (Fig. 1) [48–51]. Predominant RNA modifications include 7-methylguanosine (m7G), 5-methylcytosine (m5C), N1-methyladenosine (m1A), and N6-methyladenosine (m6A) [52–56]. Other widespread RNA modifications, such as pseudouridine (Ψ) and adenosine-to-inosine (A-to-I) editing, are detected in most RNA types [57–60].

Numerous studies have demonstrated the integral role of RNA modifications in diverse biological processes, including stem cell differentiation, tissue development, and responses to external stress [61–63]. Aberrant levels of RNA modifications and their regulatory proteins, whether higher or lower than normal, are frequently associated with cancer progression, drug resistance, and disease relapse. Normal reference levels are typically based on each type of healthy tissue or cell lines [64–68]. Specifically, RNA modifications may drive drug

response in various cancers by modulating drug transport and metabolism, target receptors, cancer stemness, and DNA repair [69–72]. Targeting RNA modifications offers a promising strategy for enhancing traditional anti-cancer treatments by inhibiting overactive enzymes and activating those that are underactive [73–76]. However, the majority of RNA modification functions in pathological processes are intricately linked to the unique disease environment, presenting challenges in targeting RNA modifications for cancer treatment [62, 77, 78]. Understanding the role of RNA modifications in drug resistance can facilitate the development of novel strategies to overcome drug resistance and improve cancer treatment outcomes [79–82]. This review summarizes recent research on the role of RNA modifications, specifically m6A, m1A, m5C, m7G, Ψ , and A-to-I editing, in cancer therapeutic resistance. Additionally, it explores the mechanisms underlying RNA modifications associated with drug resistance and discusses strategies for targeting these modifications to reverse drug resistance and improve patient prognosis.

Overview of key RNA modifications

Adenosine methylation

N6-methyladenosine modification

m6A, a significant epigenetic modification, involves adding a methyl group to the nitrogen atom at the sixth position of adenosine. This modification is present in various RNA species, including messenger RNAs (mRNAs), long non-coding RNAs (lncRNAs), ribosomal RNAs (rRNAs), and polyadenylated RNAs [83–87]. Predominantly occurring in the 3'-untranslated regions (3'-UTRs) and near mRNA stop codons, m6A is regulated by specific methyltransferases (“writers”), demethylases (“erasers”), and m6A-binding proteins (“readers”) [43, 88–91]. The core methyltransferase complex comprises Methyltransferase-like 3 (METTL3) and Methyltransferase-like 14 (METTL14), with METTL3 serving as the catalytic core. Additional proteins such as Wilms tumor 1-associated protein (WTAP), VIR-like m6A methyltransferase associated (VIRMA), RNA-binding motif protein 15 (RBM15), and zinc finger CCCH-type containing 13 (ZC3H13) support this complex, facilitating the co-transcriptional deposition of m6A on nascent pre-mRNAs [73, 92–97]. Demethylation is executed by enzymes such as Fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5) [98–101]. Reader proteins recognizing and interpreting m6A marks include members of the YTH domain family (YTHDF1-3, YTHDC1-2) and others like insulin-like growth factor 2 mRNA-binding proteins (IGFBPs), Musashi2 (MSI2), Proline-rich coiled-coil containing protein 2 A (PRRC2A), and Heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1) [102–106].

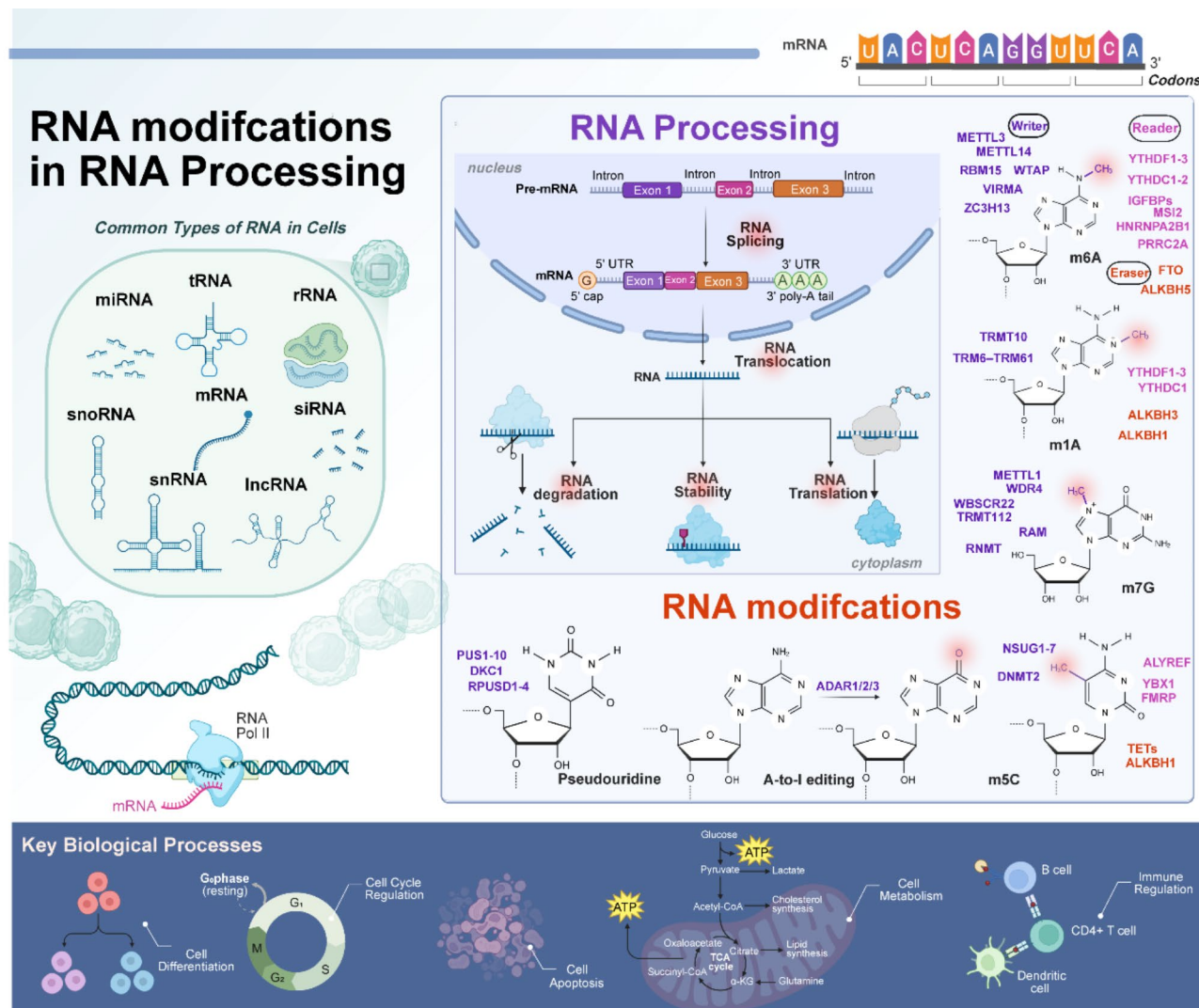


Fig. 1 Overview of main RNA modifications closely associated with cancer development. The most critical RNA modifications implicated in tumorigenesis include 7-methylguanosine (m7G), 5-methylcytosine (m5C), N1-methyladenosine (m1A), N6-methyladenosine (m6A), pseudouridine (Ψ), and adenosine-to-inosine (A-to-I) editing. These modifications alter the chemical structure of RNAs, directly affecting gene expression and various biological processes. RNA modifications are dynamic and often reversible. “Writer” proteins add chemical groups to RNA molecules, thereby enhancing or modifying their function. “Readers” identify and bind to these modified RNAs, influencing subsequent RNA processing steps such as splicing, localization, export, translation, stability, and degradation. Conversely, “erasers” remove RNA modifications, potentially restoring the original RNA functions. The intricate interplay among writers, readers, and erasers is essential for cellular responses and adaptations, particularly in cancer cells

N1-methyladenosine modification

m1A, an essential internal RNA modification, involves adding a methyl group to the nitrogen atom at the first position of adenosine [107–111]. This modification is found in various RNA types, including transfer RNAs (tRNAs), rRNAs, mRNAs, lncRNAs, and mitochondrial RNAs [112–115]. m1A is particularly enriched near the start codon and just upstream of the first splice site, playing a pivotal role in the initiation of translation [116–119]. The methyltransferase complex responsible for installing m1A in tRNAs includes tRNA methyltransferase 10 homolog A (TRMT10) and the TRM6-TRM61 complex

[108, 120–124]. The AlkB family of demethylases, such as ALKBH1 and ALKBH3, reverse the m1A modification, with ALKBH3 being the sole enzyme known to remove m1A from mRNAs [125–129]. YTH domain-containing proteins, including YTHDF1-3 and YTHDC1, primarily recognize and bind to m1A-modified RNAs [130, 131].

Other RNA modifications

5-methylcytosine Modification

5-Methylcytosine (m5C) is a prevalent and extensively studied RNA modification [132–135]. It involves the addition of a methyl group to the fifth carbon of cytosine,

found in various RNA classes, including tRNAs, mRNAs, rRNAs, and enhancer RNAs (eRNAs) [136–140]. m5C is particularly enriched near stop codons and within coding sequences in mRNAs and at loop structures in tRNAs. This modification is primarily catalyzed by the NOL1/NOP2/SUN domain (NSUN) family of SAM-dependent methyltransferases and DNA methyltransferase-like 2 (DNMT2) [137, 141, 142]. In mammalian cells, the ten-eleven translocation (TET) family and ALKBH1 are responsible for reversing m5C modification [143–145]. Aly/REF export factor (ALYREF) and Y-box binding protein 1 (YBX1) act as reader proteins that specifically interact with m5C-modified RNAs, playing pivotal roles in regulating RNA metabolism and function [136, 146–148]. Fragile X mental retardation protein (FMRP) is another m5C reader that coordinates between m5C writers and erasers, facilitating transcription-coupled homologous recombination [149–151].

7-methylguanosine Modification

N7-methylguanosine (m7G) is a key RNA modification primarily found at the 5' cap of eukaryotic mRNAs, and also internally in rRNAs, tRNAs, and microRNAs (miRNAs) [152–156]. This modification involves the addition of a methyl group to the N7 position of ribo-guanosine [157–160]. Methyltransferase-like 1 (METTL1), along with its cofactor WD repeat domain 4 (WDR4), is the primary enzyme responsible for m7G modification in mammals [161–165]. In human 18S rRNA, the m7G modification at position 1639 is mediated by the Williams–Beuren syndrome chromosomal region 22 (WBSR22)–TRMT112 complex [166–169]. RNA guanine-7 methyltransferase (RNMT) and RNMT-activating miniprotein (RAM) specifically target the 5' cap of mRNAs for m7G modification [170–172]. To date, no enzymes responsible for the removal or specific recognition of m7G have been identified [173, 174].

Pseudouridine modification

Pseudouridine (Ψ) is the most abundant RNA modification in various RNA classes in humans, including tRNAs, mRNAs, small nuclear RNAs (snRNAs), and other non-coding RNAs [175–178]. Ψ , an isomer of uridine, is formed by relocating the N-C glycosidic bond from the sixth to the fifth carbon position [179–181]. This modification is enriched within the coding region and 3'-UTR of mRNAs [182, 183]. Of the 14 known pseudouridine writers, dyskerin pseudouridine synthase 1 (DKC1) is part of a small nucleolar ribonucleoprotein complex and primarily targets rRNAs, snRNAs, small nucleolar RNAs (snoRNAs), and the non-coding RNA component of telomerase (TERC) [184–188]. Currently, there are no known enzymes that erase or specifically recognize pseudouridine modifications.

Adenosine-to-inosine editing

Adenosine-to-inosine (A-to-I) editing is among the most prevalent co-transcriptional and post-transcriptional RNA modifications in mammals [189–193]. Unlike reversible modifications such as m6A and m5C, A-to-I editing induces a permanent alteration within RNAs [194–197]. This modification is mediated by a family of enzymes known as adenosine deaminases acting on RNAs (ADARs), which preferentially edit adenines flanked by 5'-uridine and 3'-guanosine [198–200]. The primary targets of A-to-I editing are double-stranded RNAs (dsRNAs) derived from inverted Alu repetitive elements (Alu dsRNAs), which are abundant in the human genome [201–204]. A-to-I editing occurs at various RNA locations, leading to diverse functional outcomes crucial for cellular dynamics and genetic regulation [205, 206].

Association of aberrant RNA modifications with Drug Resistance

Aberrant RNA modifications have been linked to the development of various human diseases, including cancer [207–211]. Loss-of-function mutations in genes encoding RNA modification regulators, as well as point mutations that hinder proper RNA modifications, contribute to RNA modification abnormalities (Fig. 2) [47, 212–215]. Multiple factors lead to the deregulation of RNA modifications, consequently affecting drug resistance through mechanisms such as changes in gene expression, metabolic reprogramming, and immune evasion. These alterations influence the sensitivity of tumor cells to chemotherapy, targeted therapy, and immunotherapy (Table 1) (Fig. 3) [70, 216–219].

Aberrant RNA modifications interfere with gene expression by altering the stability and translation efficiency of mRNAs encoding proteins essential for DNA repair, cell cycle control, and apoptosis. This interference leads to increased DNA mutation frequency and genomic instability [70, 149, 217, 218, 269]. For instance, abnormal modifications in the cap, tail, and internal regions of tumor suppressor gene RNA can disrupt transcription, thereby promoting tumorigenesis and resistance to anti-cancer drugs [270–273]. Dysregulation of RNA modifications also affects the expression of drug-metabolizing enzymes or transporters involved in drug metabolism and efflux, such as ATP-binding cassette (ABC) transporters, enhancing drug efflux and reducing intracellular drug concentration [274–277].

Cancer cells can modify metabolic processes to support rapid, uncontrolled growth and proliferation [278–282]. RNA modifications critically impact metabolic pathways involved in cancer cell survival under drug-induced stress. Increasing evidence suggests that RNA modifications influence the expression and activity of key enzymes and transcription factors involved in

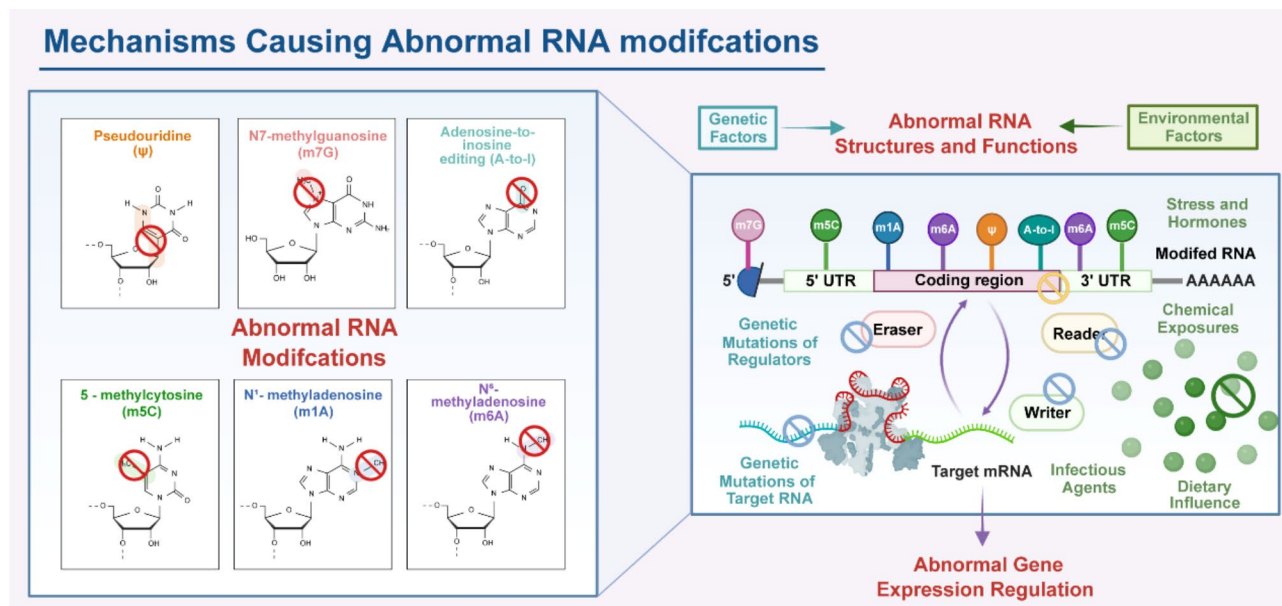


Fig. 2 Mechanisms of abnormal RNA modifications. Aberrant RNA modifications can drive cancer progression through complex genetic and environmental interactions within the tumor microenvironment. These modifications often result from genetic mutations in enzymes that add or remove methyl groups, or in RNA-binding proteins, as well as from mutations in target genes that disrupt normal RNA modification processes

the Warburg effect, enabling cancer cells to prefer glycolysis over oxidative phosphorylation [278, 283, 284]. This metabolic shift supports rapid cancer cell growth and contributes to drug resistance by enhancing cellular adaptation to the toxic effects of chemotherapy.

RNA modifications significantly contribute to immune evasion, indirectly promoting drug resistance [285–288]. Studies have shown that FTO enhances the self-renewal and immune evasion capabilities of cancer stem cells (CSCs) [289–291]. Reducing FTO expression through genetic manipulation or pharmacological intervention to lower immune checkpoint gene expression has demonstrated potent therapeutic effects against various cancer types [65, 101]. In the innate immune system, cells detect pathogens *via* encoded receptors, primarily RIG-I-like receptors (RLRs), endosomal toll-like receptors (TLRs), and protein kinase R (PKR) [292–294]. The m6A modification can disrupt RIG-I-mediated activation of innate immunity, aiding cancer cells in evading immune responses. Additionally, A-to-I RNA editing is crucial for immune system development, influencing T and B cell maturation by affecting innate immune tolerance to self-RNAs [295–298]. Antigen presentation is vital for the immune system's recognition of cancer cells. Certain RNA modifications impede antigen presentation in cancer cells, reducing the visibility of antigens to immune cells [299–301]. For instance, the loss of YTHDF1 in dendritic cells (DCs) enhances the cross-presentation of tumor antigens and activation of CD8⁺T cells, thereby improving the immune response to cancer [266, 302]. The intricate interplay of RNA modifications in cancer

cells underscores their importance in immune evasion, highlighting potential therapeutic targets to enhance immunotherapy efficacy [303–306].

The diverse impacts of RNA modifications on gene expression, metabolic processes, and immune system interactions underscore their critical role in the development of drug resistance in cancer cells. Targeting these RNA modifications offers a promising strategy for overcoming resistance and improving the efficacy of existing cancer therapies [307, 308].

Profiles and mechanisms of aberrant RNA modifications in Chemotherapy Resistance in Cancer

Chemotherapy effectively suppresses tumor cell proliferation, but resistance frequently leads to treatment failure, promoting relapse or metastasis [309–311]. Common chemotherapeutic agents include alkylating agents like cyclophosphamide; antimetabolites such as 5-fluorouracil and cytarabine; DNA crosslinkers like cisplatin and carboplatin; anthracycline antibiotics including doxorubicin, idarubicin, and mitoxantrone; anti-microtubule agents such as paclitaxel and docetaxel; topoisomerase inhibitors like etoposide; nucleoside analogs such as gemcitabine; DNA methyltransferase inhibitors like 5-azacytidine; and proteasome inhibitors such as bortezomib, melphalan, and carfilzomib. These drugs exert their therapeutic effects through distinct mechanisms. The advent of immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 has revolutionized cancer treatment [312–314]. However, resistance can arise from complex interactions between these inhibitors and the

Table 1 Expression profiles and roles of RNA modifications in drug resistance in cancer

	RNA modification	Gene	Type	Expression alteration	Role	RNA target	Downstream targets	Year	Ref.
PC	m6A	ALKBH5	Eraser	Down-regulation	Anti-oncogene	mRNA	WIF-1	2020	[220]
PC	m6A	ALKBH5	Eraser	Up-regulation	Oncogene	lncRNA	lncRNA DDIT4-AS1	2022	[221]
PC	m6A	METTL3	Writer/Reader	Up-regulation	Oncogene	lncRNA	lncRNA ANRIL	2022	[222]
PC	m6A and A-to-I	METTL3	Writer	Down-regulation	Anti-oncogene	dsRNA	METTL3/dsRNA/RLRs	2023	[223]
CRC	m6A	METTL3/IGF2BP1	Writer/Reader	Up-regulation	Oncogene	mRNA	Section 62	2021	[224]
CRC	m6A	METTL3	Writer	Up-regulation	Oncogene	miRNA	pre-miR-181d	2022	[225]
CRC	m6A	FTO/YTHDF2	Eraser/Reader	Up-regulation	Oncogene	mRNA	SIVA1	2023	[226]
CRC	m6A	METTL3/METTL14	Writer	Up-regulation	Oncogene	mRNA	STAT1 and IRF1	2020	[227]
CRC	m7G	METTL1	Writer	Down-regulation	Anti-oncogene	miRNA	miR-149-3p	2019	[228]
GC	m6A	HNRNPA2B1	Reader	Up-regulation	Oncogene	lncRNA	lncRNA NEAT1	2024	[229]
GC	m6A	METTL3	Writer	Up-regulation	Oncogene	mRNA	ARHGAP5	2019	[230]
GC	m6A	MSI2	Reader	Up-regulation	Oncogene	mRNA	c-Myc	2022	[231]
HCC	m6A	METTL14	Writer	Up-regulation	Oncogene	mRNA	HNF3y	2020	[232]
HCC	m6A	METTL3/YTHDF1	Writer/Reader	Down-regulation	Anti-oncogene	mRNA	FOXO3	2020	[233]
HCC	m7G	METTL1/WDR4	Writer	Up-regulation	Oncogene	tRNA	/	2023	[164]
HCC	m7G	WDR4	Writer	Up-regulation	Oncogene	tRNA	TRIM28	2023	[234]
BC	m6A	METTL3	Writer	Up-regulation	Oncogene	mRNA	EGF	2022	[235]
BC	m6A	METTL3	Writer	Up-regulation	Oncogene	miRNA	pri-miR-221-3p	2021	[236]
BC	m6A	ALKBH5	Eraser	Up-regulation	Oncogene	mRNA	FOXO1	2024	[237]
BC	m6A	ALKBH5/YTHDF2	Eraser/Reader	Up-regulation	Oncogene	lncRNA	LINC00115	2024	[238]
OC	m6A	YTHDF1	Reader	Up-regulation	Oncogene	mRNA	TRIM29	2020	[239]
OC	m6A	ALKBH5/YTHDF2	Eraser/Reader	Up-regulation	Oncogene	mRNA	JAK2	2021	[240]
CC	m6A	ZC3H13	Writer	Up-regulation	Oncogene	mRNA	CENPK	2022	[241]
BCa	m6A	ALKBH5	Eraser	Down-regulation	Anti-oncogene	mRNA	CK2α	2021	[242]
BCa	m6A	WTAP	Writer	Up-regulation	Oncogene	mRNA	TNFAIP3	2021	[243]
BCa	m6A	NAT10	Writer	Up-regulation	Oncogene	mRNA	AHNAK	2023	[244]
CRPC	m6A	RBM15	Writer	Up-regulation	Oncogene	mRNA	TPM1	2023	[245]
Leukemia	m6A	IGF2BP1	Reader	Up-regulation	Oncogene	mRNA	ALDH1A1, HOXB4, and MYB	2020	[246]
Leukemia (AML)	m6A	METTL3	Writer	Up-regulation	Oncogene	mRNA	ITGA4	2022	[247]
Leukemia (AML)	m7G	/	/	Up-regulation	Oncogene	circRNA	AML resistance-associated genes	2023	[248]
Leukemia (AML) and MDS	m5C	NSUN1, NSUN3, and DNMT2	Writer/Reader	/	/	/	/	2018	[249]
Leukemia (CML)	m6A	METTL3	Writer	Up-regulation	Oncogene	mRNA	PTEN	2021	[250]
MM	m6A	METTL7A	Writer	Up-regulation	Oncogene	lncRNA	LOC606724 and lncRNA SNHG1	2022	[251]
NPC	m6A	METTL5/TRMT112	Writer	Up-regulation	Oncogene	rRNA	18 S rRNA	2023	[252]
NPC	m7G	METTL1/WDR4	Writer	Up-regulation	Oncogene	tRNA	WNT	2022	[253]
Osteosarcoma	m7G	METTL1/WDR4	Writer	Up-regulation	Oncogene	tRNA	/	2023	[254]
Osteosarcoma	m5C	NSUN2	Writer/Reader	Up-regulation	Oncogene	mRNA	AXL, NOTCH2, and YAP1	2023	[255]

Table 1 (continued)

	RNA modification	Gene	Type	Expression alteration	Role	RNA target	Downstream targets	Year	Ref.
Leukemia	m6A	FTO	Eraser	Up-regulation	Oncogene	/	m6A methylation	2018	[256]
LC	m6A	METTL3/MTAP	Writer	Up-regulation	Oncogene	mRNA	c-MET	2020	[257]
LC	m6A	METTL3	Writer	Up-regulation	Oncogene	mRNA	LC3B, ATG5, and ATG7	2020	[258]
LC	m6A	METTL3	Writer	Up-regulation	Oncogene	mRNA	DCP2	2023	[259]
LC	m5C	NSUN2/YBX1	Writer/Reader	Up-regulation	Oncogene	mRNA	OSOX1	2023	[260]
LC	A-to-I	/	/	Down-regulation	Anti-oncogene	mRNA	miR-411-5p	2023	[261]
LC	m6A	METTL3	Writer	Up-regulation	Oncogene	lncRNA	lncRNA SNHG17	2022	[262]
LC	m6A	METTL7B	Writer	Up-regulation	Oncogene	mRNA	GPX4, HMOX1 and SOD1	2021	[263]
LC	m6A	METTL3/YTHDF2	Writer/Reader	Up-regulation	Oncogene	mRNA and lncRNA	miR-146a and TUSC7	2021	[264]
Melanoma	m6A	METTL3	Writer	Up-regulation	Oncogene	mRNA	EGFR	2021	[265]
Melanoma	m6A	YTHDF1	Reader	Up-regulation	Oncogene	mRNA	mRNAs that encode lysosomal proteases	2019	[266]
Melanoma	m6A	FTO/YTHDF2	Eraser/Reader	Up-regulation	Oncogene	mRNA	PD-1, CXCR4, and SOX10	2019	[267]
Immunologically 'cold' tumor	m5C	NSUN2	Writer	Up-regulation	Oncogene	mRNA	TREX2	2023	[268]

TME. Resistance to targeted therapies remains a significant challenge, affecting the prognosis of various tumors, including hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC) [315–319]. Therapeutic resistance in cancer involves a complex interplay of factors such as oncogene activation, impaired DNA repair, hypoxic TME, and metabolic alterations. CSCs significantly contribute to therapeutic resistance due to their self-renewal capabilities, aberrant differentiation, and enhanced drug efflux [320–323]. Recent studies on RNA modifications have revealed that epigenetic mechanisms play a pivotal role in developing therapeutic resistance in cancer [324, 325]. Investigating the patterns and mechanisms of aberrant RNA modifications in cancer can enhance the understanding of therapeutic resistance and provide novel avenues for developing effective therapeutic strategies (Table 2).

Effects of abnormal RNA modifications on chemotherapy resistance in gastro-intestinal cancers

5-Fluorouracil (5-FU) and the pyrimidine analog gemcitabine are widely used anti-nucleotide metabolism drugs in treating digestive system cancers, particularly pancreatic cancer (PC). Long non-coding RNAs (lncRNAs) play a critical role in maintaining cancer stemness, contributing to 5-FU resistance in PC. METTL3 enhances m6A modification in the lncRNA FOXD1-AS1 through a YTHDF1-dependent mechanism in MIA cells. Overexpressed FOXD1-AS1 then promotes self-renewal and 5-FU resistance in PC cells by acting as a competing endogenous RNA (ceRNA) that sponges miR-570-3p, resulting in increased expression of secreted phosphoprotein 1 (SPP1). Additionally, studies using patient-derived xenograft (PDX) models have highlighted FOXD1-AS1's potential as a biomarker for predicting 5-FU treatment efficacy in PC [326]. ALKBH5 has dual roles in gemcitabine resistance in PC, either promoting or inhibiting drug resistance depending on the m6A modification of various downstream molecules. For example, ALKBH5 downregulation is linked to increased gemcitabine resistance and poor clinical outcomes. ALKBH5 demethylates WIF-1 mRNA to promote its transcription, inhibiting the Wnt signaling pathway in AsPC-1 and PANC-1 cells. This inhibition increases gemcitabine sensitivity, reducing the proliferative, colony-forming, and migratory abilities of PC cells, ultimately suppressing tumor growth and liver metastasis [220]. Conversely, ALKBH5 mediates m6A modification in the lncRNA DNA damage-inducible transcript 4 antisense transcript 1 (DDIT4-AS1), increasing its expression in PC cells. Upregulated DDIT4-AS1 disrupts DDIT4 mRNA stability and activates the mTOR pathway, enhancing cancer stemness and reducing gemcitabine sensitivity [221]. Serine/arginine-rich splicing factor 3 (SRSF3) and METTL3

Abnormal RNA Modification in Cancer Development

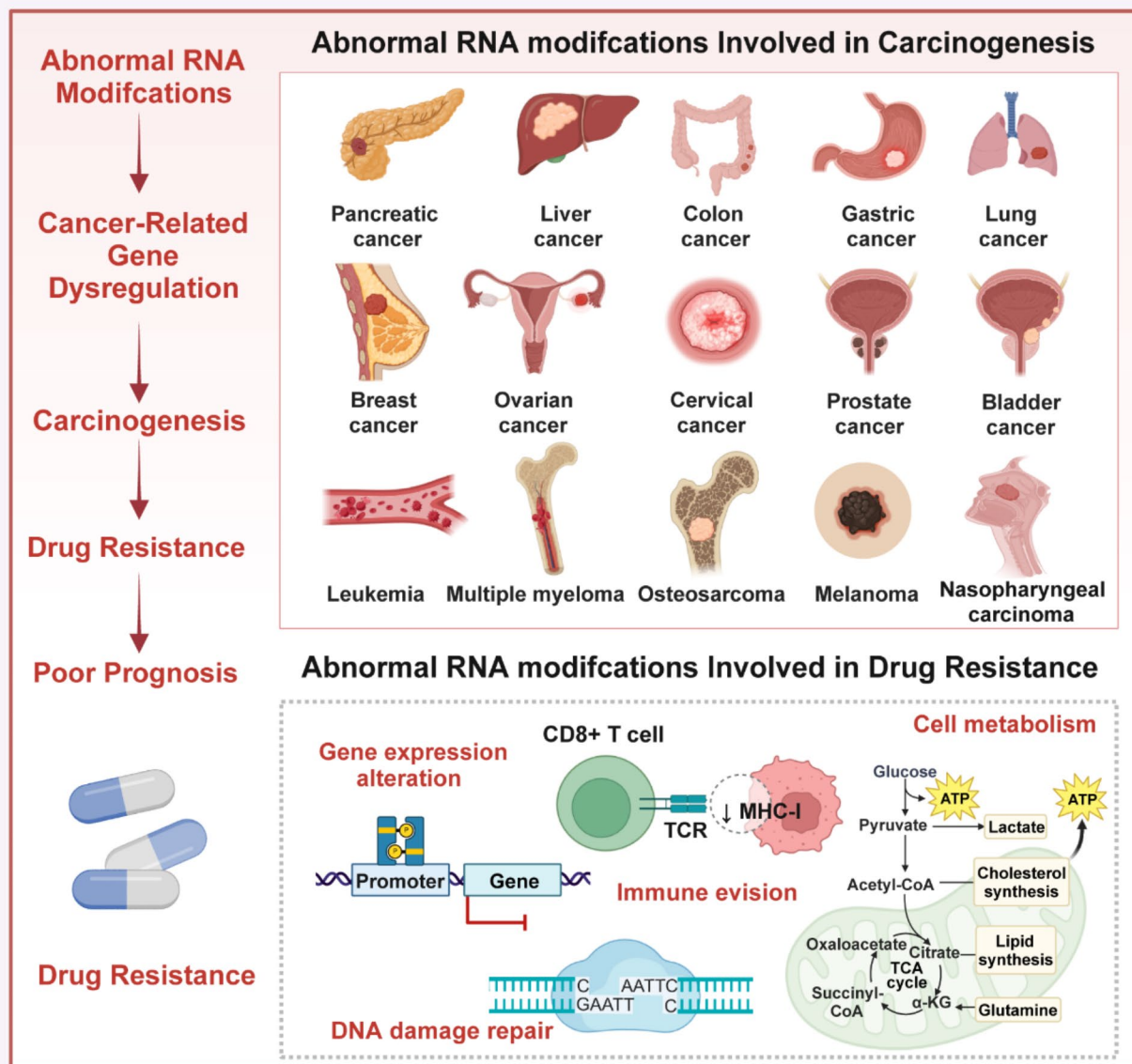


Fig. 3 General Mechanisms of abnormal RNA modifications in drug resistance. Aberrant RNA modifications and their regulators are frequently linked to chemotherapy resistance in various cancers, including those of the digestive, genitourinary, and respiratory systems, as well as hematologic malignancies. These modifications can alter gene expression, affect DNA damage repair (DDR), and induce immune evasion, thereby contributing to drug resistance. Collectively, these drug resistance-related processes accelerate cancer progression, underscoring the significant role of RNA modifications in shaping the malignant behavior of cancer cells and influencing therapeutic outcomes

induce m6A modification-related splicing of the lncRNA ANRIL in Panc1 and BXPC3 cells. This modification enables ANRIL to form a DNA homologous recombination (HR) repair complex with Ring finger protein 1B (Ring1B) and zeste homolog 2 (EZH2), enhancing DNA repair capabilities and gemcitabine resistance in PC cells [222]. RNA modifications also influence 5-FU resistance in colorectal cancer (CRC). METTL3 is crucial for

aberrant m6A modifications contributing to chemoresistance in CRC. High m6A levels are observed in CRC tissues and cell lines. IGF2BP1 binds to METTL3-modified Sect. 62 mRNA, enhancing its stability and expression in CRC cells. Upregulated Sect. 62 interacts with β -catenin to activate the Wnt signaling pathway, which enhances stemness and chemoresistance in CRC [224]. Exosomal miR-181d-5p derived from cancer-associated fibroblasts

Table 2 Mechanisms of RNA modifications involved in drug resistance in cancer

RNA modification	Cancer type	Drug	Gene	Downstream targets	Mechanisms	Cell lines	Clinical samples and in vivo model	Year	Ref.
m6A	PC	gemcitabine	ALKBH5	WIF-1	ALKBH5/WIF-1	A5PC-1 and PANC-1 cells	xenograft models	2020	[220]
m6A	PC	gemcitabine	ALKBH5	lncRNA DDIT4-AS1	ALKBH5/lncRNA DDIT4-AS1/DDIT4/mTOR	BxPC3 and SW1990 cells	40 pairs of PDAC tissues, and xenograft models	2022	[221]
m6A	PC	gemcitabine	METTL3	lncRNA ANRIL	SRSF3/METTL3/lncRNA ANRIL/Ring1B/EZH2	Panc1 and BxPC3 cells	143 PDAC tissues and non-tumorous tissues, and xenograft models	2022	[222]
m6A	PC	5-FU	METTL3/γTHDF1	lncRNA FOXD1-AS1	METTL3/γTHDF1/lncRNA FOXD1-AS1/miR-570-3p/SPP1	MIA Paca-2 and A5PC-1 cells	30 PC tissues, and xenograft models	2024	[326]
m6A and A-to-I	PC	Anti-PD-1 immunotherapy	METTL3	METTL3/dsRNA/RLRs	METTL3/dsRNA/RLRs	PANC-1, Capan-1, CFPAC-1, and A5PC-1 cells	xenograft models	2023	[223]
m6A	CRC	5-FU	METTL3/IGF2BP1	Section 62	METTL3/sect. 62/Wnt/β-catenin	DLD1 and SW480 cells	102 CRC tissues and non-tumorous colorectal tissues, and xenograft models	2021	[224]
m6A	CRC	5-FU	METTL3	pre-miR-181d	METTL3/DGCR8/miR-181d-5p/NCALD	CAF5, HCT116, and HT29 cells	141 CRC tissues and non-tumorous colorectal tissues, and xenograft models	2022	[225]
m6A	CRC	5-FU	FTO/γTHDF2	SIVA 1	FTO/γTHDF2/SIVA 1	HCT-8 and HCT-116 cells	3 pairs of normal, primary, and resistant tissues from CRC patients, and xenograft models	2023	[226]
m7G	CRC	cisplatin	METTL1	miR-149-3p	METTL1/miR-149-3p/S100A4/p53	HCT116, SW480 and SW620 cells	/	2019	[228]
m6A	CRC	Anti-PD-1 immunotherapy	METTL3/METTL14	STAT1 and IRF1	METTL3/METTL14/INF-γ/STAT1/IRF1	CT26	human pMMR-MSI-L CRC tissues, and xenograft models	2020	[227]

Table 2 (continued)

RNA modification	Cancer type	Drug	Gene	Downstream targets	Mechanisms	Cell lines	Clinical samples and In vivo model	Year	Ref.
m6A	GC	5-FU	HNRNP2B1	lncRNA NEAT1	lncRNA NEAT1/lncRNA NEAT1/Wnt/ β -catenin	AGS, MGC803, BGC823, and SGC7901 cells	75 cases of GC tissues and paired adjacent normal tissues, and 28 cases of unpaired GC tissues, and xenograft and xenograft models	2024	[229]
m6A	GC	cisplatin, ADR, and 5-FU	METTL3	ARHGAP5	lncRNA ARHGAP5-AS1/ METTL3/ARHGAP5	SGC7901 and BGC823 cells	/	2019	[230]
m6A	GC	cisplatin	MSI2	c-Myc	LINC00942/MSI2/ c-Myc	SGC7901 and BGC823 cells	xenograft models	2022	[231]
m6A	HCC	sofafenib	METTL14	HNF3 γ	METTL14/HNF3 γ / OATP1B1/OATP1B3	HCCLM3 and Huh7 cells	580 HCC tissues and corresponding paracancerous tissues, and xenograft models	2020	[232]
m6A	HCC	sofafenib	METTL3/THDF1	FOXO3	METTL3/THDF1/ FOXO3	SMMC-7721, Bel-7402, and HepG-2	63 pairs of HCC tissues and peritumoral normal tissues, and xenograft models	2020	[233]
m7G	HCC	lenvatinib	METTL1/WDR4	/	METTL1/WDR4/ Tina	PLC/PRF/5, Hep3B, HepG2, and HepG2 cells	108 HCC tissues and peritumor tissues, organoids, hydrodynamic injection mouse models, subcutaneous implantation mouse models, and orthotopic xenograft mouse models	2023	[164]
m7G	HCC	lenvatinib	WDR4	TRIM28	WDR4/TRIM28	Huh7, Hep3B, and PLC/PRF/5 cells	/	2023	[234]
m6A	BC	ADR	METTL3	EGF	METTL3/THDC1/ EGF/RAD51	MCF-7 and MB-231 BC cells	xenograft models	2022	[235]
m6A	BC	ADR	METTL3	pri-miR-221-3p	METTL3/miR-221-3p/ HIPK2/Che-1	MCF-7 BC cells	xenografts models	2021	[236]
m6A	BC	ADR	ALKBH5	FOXO1	ALKBH5/FOXO1/ SOD2/ROS	MDA-MB-231 and BT549 cells	50 BC tissues, and xenograft models	2024	[237]

Table 2 (continued)

RNA modification	Cancer type	Drug	Gene	Downstream targets	Mechanisms	Cell lines	Clinical samples and In vivo model	Year	Ref.
m6A	BC	PTX	ALKBH5/YTHDF2	LINC00115	HIF1 α /ALKBH5/YTHDF2/LINC00115	MDA-MB-231 and BT549 cells	metastatic lymph nodes from 118 BC clinical specimens, and xenograft models	2024	[238]
m6A	OC	cisplatin	YTHDF1	TRIM29	YTHDF1/TRIM29	SKOV3/DDP and A2780/DDP cells	24 OC tissues, and xenograft models	2020	[239]
m6A	OC	cisplatin	ALKBH5/YTHDF2	JAK2	ALKBH5/HOXA10/YTHDF2/JAK2/STAT3	A2780/DDP and HO8910/DDP cells	57 OC tissues, and xenograft models	2021	[240]
m6A	CC	cisplatin and carboplatin	ZC3H13	CENPK	ZC3H13/CENPK/SOX6/Wnt4p53	HeLa and SiHa	119 CC tissues and 35 adjacent normal tissues, and xenograft models	2022	[241]
m6A	BCa	cisplatin	ALKBH5	CK2 α	ALKBH5/CK2 α /glycolysis	5637 and T24 cells	28 pairs of BCa tissues and adjacent normal tissues, and xenograft models	2021	[242]
m6A	BCa	cisplatin	WTAP	TNFAIP3	circ0008399/WTAP/TNFAIP3	EJ and T24T cells	72 pairs of BCa tissues and adjacent normal tissues	2021	[243]
ac4C	BCa	cisplatin	NAT10	AHNAK	NAT10/AHNAK	UM-UC-3 and T24 cells	BCa tissues and adjacent normal tissues, BCa chemotherapy resistant tissues and sensitive tissues, organoids, and xenograft models	2023	[244]

Table 2 (continued)

RNA modification	Cancer type	Drug	Gene	Downstream targets	Mechanisms	Cell lines	Clinical samples and In vivo model	Year	Ref.
m6A	CRPC	docetaxel	RBM15	TPM1	AZGP1p2/UBA1/RBM15/TPM1	PC3 and DU145 cells	499 pairs of BCa tissues and adjacent normal tissues from TCGA database, organoids derived from CRPC with docetaxel resistance patients, and tail vein injection mouse models derived from PC3 and DU145 cells	2023	[245]
m6A	Leukemia	ATRA, doxorubicin, cytarabine, and cyclophosphamide	IGF2BP1	ALDH1A1, HOXB4, and MYB	IGF2BP1/ALDH1A1/HOXB4/MYB	K562, 697(EU3), and HL60/S4 cells	xenograft models	2020	[246]
m6A	Leukemia (AML)	IDA	METTL3	ITGA4	METTL3/ITGA4	THP-1, Kasumi-1, and HL-60 cells	13 bone marrow mononuclear cells from patients achieved complete remission, 20 from relapsed patients, and xenograft models	2022	[247]
m6A	Leukemia	TKIs	FTO	m6A methylation	/	BCR/ABL (K562, KU812), KIT (Kasumi-1) and FLT3 (MV4-11)	14 AML PBMCs, 2018 and xenograft models	2018	[256]
m7G	Leukemia (AML)	mitoxantrone	/	AML resistance-associated genes	m7G/circRNA-miRNA-mRNA/AML resistance-associated genes	HL-60 cells	/	2023	[248]
m5C	Leukemia (AML) and MDS	5-AZA	NSUN1/NSUN3/DNMT2	/	HNRNP/NSUN3/DNMT2/5-AZA-sensitive chromatin structure; NSUN1/BRD4/5-AZA-resistant chromatin structure	M2 and 5C cells	mononuclear cells from MDS and AML bone marrows	2018	[249]
m6A	Leukemia (CML)	ADR	METTL3	PTEN	LINC00470/METTL3/PTEN	KCL22 and K562 cells	xenograft models	2021	[250]
m6A	MM	bortezomib, melphalan, carfilzomib	METTL7A	LOC606724 and lncRNA SNHG1	EZH2/METTL7A/LOC606724/lncRNA SNHG1	human MM cell line ARP-1 cells, MM.1 S, RPMI8226, and U266 cells	xenograft models	2022	[251]

Table 2 (continued)

RNA modification	Cancer type	Drug	Gene	Downstream targets	Mechanisms	Cell lines	Clinical samples and in vivo model	Year	Ref.
m6A	NPC	cisplatin and docetaxel	METTL5/TRMT112	18 S rRNA	METTL5/TRMT112/18S rRNA/H5F4b/HSP90B1/mup53	5-8 F and 6-10B cells	41 frozen NPC tissues, 4 fresh NPC tissues, 4 tissues with nasopharynx mucositis, and xenograft models	2023	[252]
m7G	NPC	cisplatin and docetaxel	METTL1/WDR4	WNT	ARN7/METTL1/WDR4/WNT/ β -catenin	5-8 F and 6-10B cells	41 NPC tissues, and xenograft models	2022	[253]
m7G	Osteosarcoma	ADR	METTL1/WDR4	/	METTL1/WDR4/rRNA/LOXL2	HOS cells	xenograft models	2023	[254]
m5C	Osteosarcoma	cisplatin and ADR	NSUN2	AXL, NOTCH2, and YAP1	DNMT1/NSUN2/AXL/NOTCH2/YAP1	U2OS, 143B, and KHOS cells	xenograft models	2023	[255]
m6A	LC	crizotinib	METTL3/WTAP	c-MET	chidamide/METTL3/WTAP/c-MET	HCC827 and H661 cells	xenograft models	2020	[257]
m6A	LC	cisplatin and etoposide	METTL3	DCP2	METTL3/DCP2/Pink1/Parkin	H69, H446, and HBE cells	58 SCLC tissues, and xenograft models	2023	[259]
m6A	LC	gefitinib	METTL3	LC3B, ATG5, and ATG7	METTL3/LC3B/ATG5/ATG7	PC9 and HCC827 cells	xenograft models	2020	[258]
m5C	LC	gefitinib	NSUN2/YBX1	OSOX1	NSUN2/YBX1/OSOX1	H1650, H1975, PC-9 and HCC2279 cells	/	2023	[260]
A-to-I	LC	gefitinib and osimertinib	/	miR-411-5p	A-to-I/miR-411-5p/MET/ERK	H1299 and H520 cells	/	2023	[261]
m6A	LC	gefitinib	METTL3	lncRNA SNHG17	METTL3/lncRNA SNHG17/EZH2/LATS2	PC9 and A549 cells	63 pairs of LC tissues and normal control lung tissues, and xenograft models	2022	[262]
m6A	LC	gefitinib and osimertinib	METTL7B	GPX4, HMOX1 and SOD1	METTL7B/GPX4/HMOX1/SOD1	PC9 and HCC827 cells	xenograft models	2021	[263]
m6A	LC	erlotinib	METTL3/YTHDF2	miR-146a and TUSC7	METTL3/YTHDF2/miR-146a/TUSC7/Notch	PC9 and HCC827 cells	xenograft models	2021	[264]
m6A	Melanoma	PLX4032	METTL3	EGFR	METTL3/EGFR/RAF/MEK/ERK	A375R cells	xenograft models	2021	[265]
m6A	Melanoma	Anti-PD-1 immunotherapy	YTHDF1	mRNAs that encode lysosomal proteases	YTHDF1/mRNAs that encoded lysosomal proteases	B16 cells	xenograft models	2019	[266]
m6A	Melanoma	Anti-PD-1 immunotherapy	FTO/YTHDF2	PD-1, CXCR4, and SOX10	autophagy/NF- κ B/FTO/YTHDF2/PD-1/CXCR4/SOX10	Mel624 and B16F10 cells	xenograft models	2019	[267]

Table 2 (continued)

RNA modification	Cancer type	Drug	Gene	Downstream targets	Mechanisms	Cell lines	Clinical samples and in vivo model	Year	Ref.
m5C	Immunologically cold tumor	Anti-PD-1 immunotherapy	NSUN2	TREX2	glucose/NSUN2/TREX2/cGAS/STING	HCC Hep3B cells, BC 4T1 cells, melanoma B16 cells, CRC CT26 cells, and PC TRAMP-C2 and PC3 cells	xenograft models	2023	[268]

(CAFs) regulates 5-FU sensitivity in CRC by targeting neurocalcin δ (NCALD), decreasing CRC cell sensitivity to 5-FU. METTL3-dependent m6A modification promotes miR-181d-5p processing by recognizing DiGeorge syndrome critical region 8 (DGCR8), highlighting the complex interplay between m6A and CAF-derived exosomes in chemoresistance [225]. Furthermore, FTO plays a significant role in promoting chemoresistance in CRC by mediating the demethylation of m6A and inducing the degradation of SIVA1 mRNA, a gene related to apoptosis, *via* a YTHDF2-dependent mechanism. Inhibiting FTO reduces 5-FU tolerance, accelerates tumor cell apoptosis, and inhibits tumor growth *via* the FTO-SIVA1 axis in both 5-FU-resistant CRC cells and tumor xenograft-bearing mouse models [226]. Overexpressed METTL1 can increase cisplatin sensitivity in CRC cells by modulating the miR-149-3p/small calcium-binding protein A4 (S100A4)/p53 axis. Specifically, METTL1 suppresses S100A4 expression and decreases cisplatin resistance in CRC cells by upregulating miR-149-3p through a p53-dependent mechanism [228].

HNRNPA2B1 is upregulated in multidrug-resistant gastric cancer (GC) cells and is linked to poor prognosis. It stabilizes the lncRNA NEAT1 *via* m6A modification, which subsequently activates the Wnt/ β -catenin signaling pathway. This activation bestows GC cells with stemness properties and heightens their resistance to 5-FU [229]. The lncRNA ARHGAP5-AS1 recruits METTL3 to stimulate m6A modification of ARHGAP5 mRNA, maintaining its stability in the cytoplasm and preventing its autophagic degradation. This process leads to resistance against cisplatin, Adriamycin (ADR), and 5-FU in GC cells [230]. Additionally, upregulated LINC00942 stabilizes and enhances c-Myc mRNA expression by interacting with MSI2 in chemo-resistant GC cells. Targeting the LINC00942–MSI2–c-Myc axis has demonstrated potential in reversing chemoresistance, promoting apoptosis, and reducing stemness in GC cells (Fig. 4) [231].

Effects of abnormal RNA modifications on chemotherapy resistance in genitourinary cancers

Since the 1970s, anthracyclines have been integral to chemotherapy, often used in neoadjuvant and combination treatments for breast cancer (BC) [327–330]. Recent studies indicate that m6A modification, particularly through METTL3, promotes chemoresistance in BC. In BC cell lines MCF-7 and MDA-MB-231, METTL3 enhances resistance to ADR by increasing homologous recombination (HR) efficiency and reducing ADR-induced DNA damage. This resistance mechanism involves METTL3-mediated m6A modification of epidermal growth factor (EGF) mRNA, which subsequently increases the expression of RAD51, a critical gene in HR. The RNA-binding protein YTHDC1

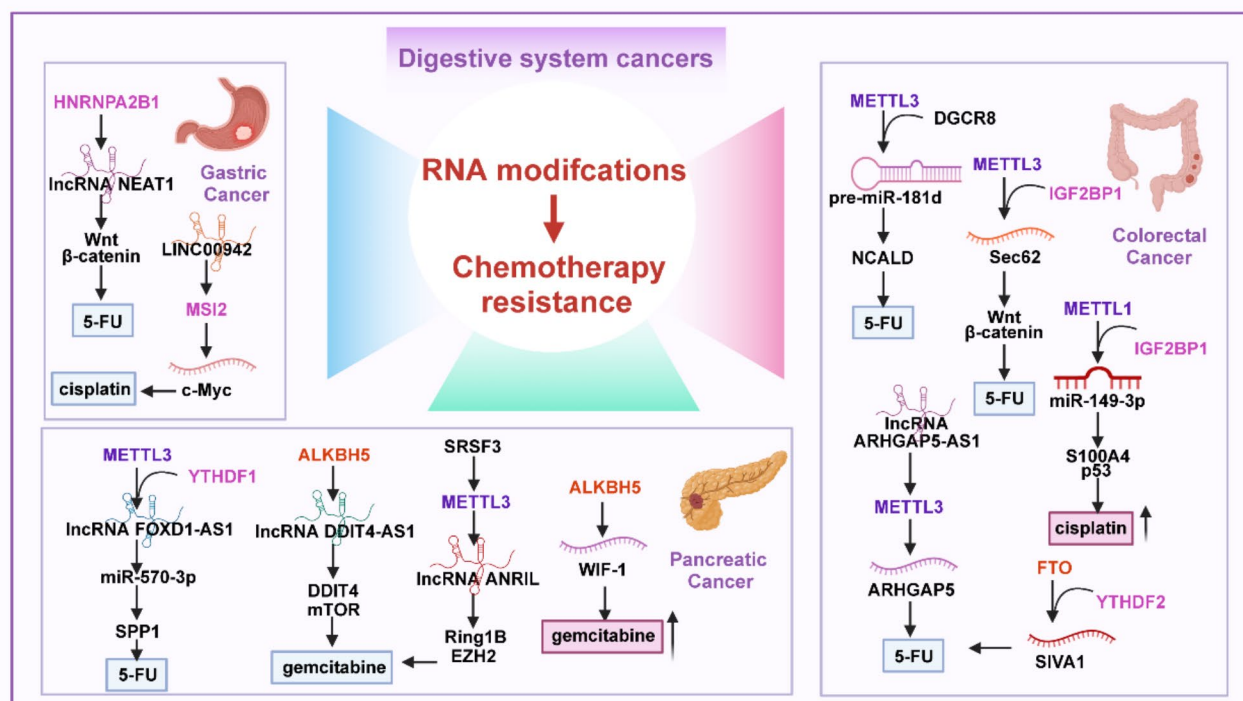


Fig. 4 Mechanisms of abnormal RNA modifications involved in chemotherapy resistance in digestive system cancers. Abnormal RNA methylation significantly contributes to chemotherapy resistance in digestive system cancers. In pancreatic cancer, METTL3-mediated m6A methylation of lncRNA FOXD1-AS1 enhances 5-FU resistance by promoting cell self-renewal through miR-570-3p sequestration. In gastric cancer, HNRNPA2B1 stabilizes lncRNA NEAT1, activating the Wnt/β-catenin pathway and increasing 5-FU resistance. Additionally, the dysregulation of RNA modification enzymes such as ALKBH5 affects gemcitabine sensitivity in pancreatic cancer by altering WIF-1 mRNA methylation and influencing the Wnt signaling pathway. These examples highlight the complex role of RNA methylation in modulating drug response and resistance across various gastrointestinal cancers

interacts with m6A-modified EGF mRNA to stabilize it, thereby enhancing HR and cellular resistance to ADR [235]. In ADR-resistant MCF-7 cells, upregulated METTL3 promotes the maturation of pri-miR-221-3p *via* m6A modification, leading to increased miR-221-3p expression. This miRNA downregulates the pro-apoptotic kinase Homeodomain-Interacting Protein Kinase 2 (HIPK2) while upregulating its target, AATF (Che-1), raising the IC₅₀ value of ADR and reinforcing resistance [236]. Forkhead box protein O1 (FOXO1)-mediated reduction of reactive oxygen species (ROS) is another key mechanism underlying ADR resistance in BC. In ADR-resistant MDA-MB-231 and BT549 cells, ALKBH5-mediated m6A demethylation enhances FOXO1 mRNA stability. Consequently, upregulated FOXO1 increases superoxide dismutase (SOD2) levels, effectively reducing intracellular ROS and maintaining cancer stemness and ADR resistance [237]. HIF1α also enhances paclitaxel (PTX) resistance by promoting BC cell stemness [331]. A key mechanism involves the upregulation of lncRNA LINC00115 in MDA-MB-231 and BT549 cells, which activates HIF1α and subsequently upregulates ALKBH5. ALKBH5 demethylates YTHDF2-mediated m6A modification of LINC00115, stabilizing its expression. This

feedback loop sustains the resistance of BC stem cells (BCSCs) to PTX and enhances their metastatic ability. Targeting this pathway with antisense oligonucleotides (ASO) against LINC00115, in combination with PTX, can effectively reduce the proliferative and invasive abilities of PTX-resistant BC cells. This strategy also significantly reduces tumor burden, prevents lung metastasis, and improves survival in animal models, representing a promising approach to overcoming PTX resistance in BC [238]. Chemotherapy resistance poses a significant challenge to improving ovarian cancer (OC) prognosis. Recent studies highlight the role of upregulated YTHDF1 in maintaining stem-like features in cisplatin-resistant OC cells. YTHDF1 enhances the translation of tripartite motif protein 29 (TRIM29) mRNA, promoting colony- and spheroid-forming abilities and invasiveness of cisplatin-resistant SKOV3/DDP and A2780/DDP cells. Upregulated TRIM29 facilitates tumorigenesis in nude mice with OC, indicating its impact on aggressiveness and chemotherapy resistance [239]. Additionally, upregulated ALKBH5 enhances epithelial cell proliferation, tumor growth, and cisplatin resistance in OC. ALKBH5 interacts with homeobox A10 (HOXA10), establishing a positive feedback loop that sustains its overexpression in

cisplatin-resistant A2780-DDP and HO8910-DDP cells. This interaction prevents YTHDF2-mediated degradation of Janus kinase 2 (JAK2) mRNA, leading to increased JAK2 expression. Activated JAK2 then phosphorylates signal transducer and activator of transcription 3 (STAT3), initiating the JAK2/STAT3 signaling pathway, which drives cell proliferation and enhances cisplatin resistance [240]. In HeLa and SiHa cervical cancer (CC) cells, ZC3H13 induces hypermethylation of centromere protein K (CENPK) mRNA, increasing CENPK expression. Upregulated CENPK interacts with SOX6, enhancing Wnt signaling and suppressing p53 signaling. These changes stimulate CC stemness and increase resistance to chemotherapeutic agents like cisplatin and carboplatin, promoting tumor growth and lung metastasis [241].

Research indicates that ALKBH5 is significantly downregulated in bladder cancer (BCa) tissues compared to healthy bladder tissues, with reduced expression linked to favorable clinical outcomes. ALKBH5 diminishes the stability of casein kinase 2 α (CK2 α) mRNA *via* an m6A-dependent mechanism, thereby lowering CK2 α expression. This reduction impairs glycolysis-related processes, including glucose utilization, lactate production, and intracellular ATP generation in BCa cells [295]. Elevated ALKBH5 levels increase BCa cells' sensitivity to cisplatin by targeting CK2 α -mediated glycolysis, thereby inhibiting cell proliferation and migration. Furthermore, this mechanism reduces tumor size and weight in BCa mouse models [242]. Circular RNAs (circRNAs) regulate m6A modification of mRNAs, influencing cisplatin resistance in BCa. Higher levels of circ0008399 and WTAP correlate with cisplatin resistance and poor clinical outcomes in BCa. circ0008399 interacts with WTAP to promote the formation of the WTAP/METTL3/METTL14 complex, enhancing m6A modification in BCa cells [296]. This interaction notably stabilizes and increases TNF alpha-induced protein 3 (TNFAIP3) mRNA expression in an m6A-dependent manner, reducing BCa cells' sensitivity to cisplatin [243]. Recent studies have revealed that cisplatin treatment can induce the upregulation of the N4-acetylcytosine (ac4C) modification writer N-acetyltransferase 10 (NAT10) through NF- κ B signaling activation [332]. Consequently, NAT10 stabilizes desmoyokin (AHNAK) mRNA, enhancing the DNA damage response (DDR) and promoting cisplatin resistance in BCa [244]. m6A sequencing of cancer tissues has shown higher overall m6A modification levels in castration-resistant prostate cancer (CRPC) compared to castration-sensitive prostate cancer (CSPC) [333, 334]. The AZGP1P2/UBA1/RBM15/TPM1 cascade is a critical pathway that enhances docetaxel sensitivity in CSPC. AZGP1 pseudogene 2 (AZGP1P2) knockdown increases the stemness of prostate cancer stem cells (PCSCs) and promotes tumor growth and metastasis, indicating AZGP1P2's essential

role in preventing docetaxel resistance. AZGP1P2 forms a complex with ubiquitin-like modifier activating enzyme 1 (UBA1) and RNA-binding motif protein 15 (RBM15), facilitating RBM15 ubiquitination and degradation. This process reduces the m6A-dependent decay of tropomyosin 1 (TPM1) mRNA, stabilizing TPM1 and inhibiting prostate cancer cell growth, migration, and metastasis. Targeting the AZGP1P2/UBA1/RBM15/TPM1 pathway may improve docetaxel therapeutic efficacy in CRPC (Fig. 5) [245].

Effects of abnormal RNA modifications on chemotherapy resistance in hematological malignancies

IGF2BP1 is highly expressed in various leukemia subtypes and is essential for maintaining leukemogenesis and promoting stemness. It enhances resistance to all-trans retinoic acid (ATRA), doxorubicin, cytarabine, and cyclophosphamide, preventing cell death and differentiation in 697(EU3) and K562 leukemia cells by post-transcriptionally regulating key self-renewal genes, including homeobox B4 (HOXB4), MYB, and aldehyde dehydrogenase 1 family member A1 (ALDH1A1) [246]. METTL3 facilitates homing and engraftment in the bone marrow (BM) and subsequent idarubicin (IDA) resistance in acute myeloid leukemia (AML) by increasing m6A modification and protein expression of integrin subunit alpha 4 (ITGA4) mRNA. The METTL3 inhibitor STM2457 has been shown to counteract the homing/engraftment capabilities of IDA-resistant AML cells, reversing their chemotherapeutic resistance [247]. Mitoxantrone-resistant AML cells exhibit more m7G sites, with resistance-related genes regulated through the circRNA-miRNA-mRNA co-expression network [248]. Enhanced m5C modification can influence 5-azacitidine (5-AZA) resistance in leukemia and myelodysplastic syndrome (MDS) by forming 5-AZA-sensitive/resistant chromatin structures on nascent RNAs in leukemia cells [249].

HNRNPK interacts with lineage-determining transcription factors (TFs) GATA1 and SPI1/PU.1, and with CDK9/P-TEFb, to recruit RNA polymerase II to nascent RNAs, forming 5-AZA-sensitive chromatin structures. In chronic myeloid leukemia (CML), LINC00470, a METTL3 regulator, enhances METTL3 recruitment to PTEN mRNA, reducing PTEN expression. This interaction activates the AKT signaling pathway, inhibiting autophagy and promoting ADR resistance in CML [250]. Multiple myeloma (MM) cells increase METTL7A activity through EZH2-mediated protein methylation. Upregulated METTL7A enriches LOC606724 and lncRNA SNHG1 in adipocyte-derived exosomes, protecting MM cells from chemotherapy-induced apoptosis and enhancing resistance to bortezomib, melphalan, and carfilzomib (Fig. 6) [335].

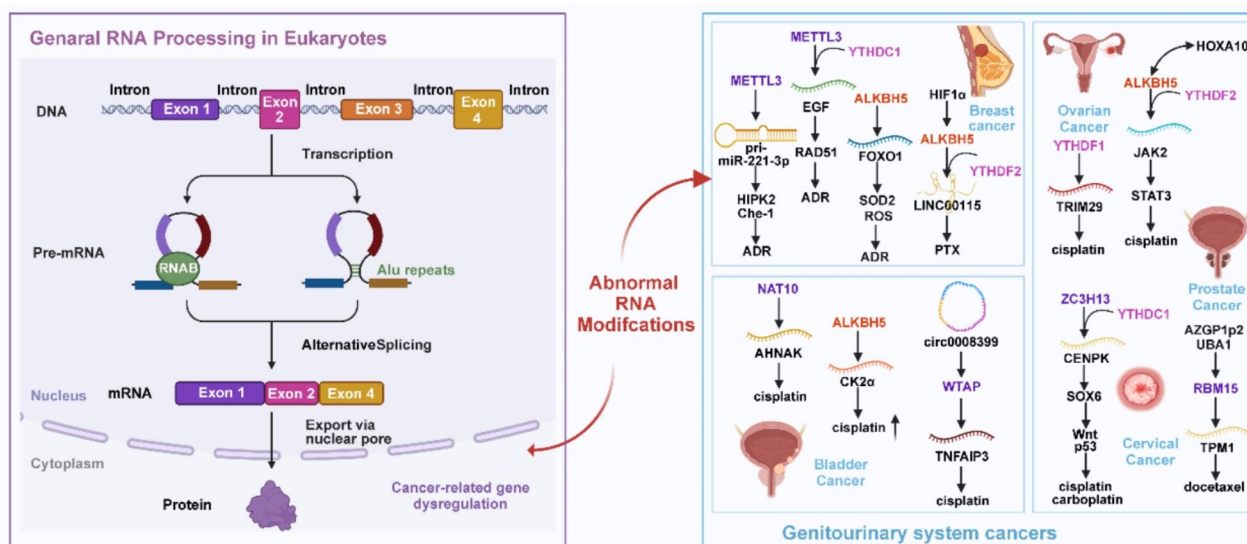


Fig. 5 Mechanisms of abnormal RNA modifications involved in chemotherapy resistance in genitourinary system cancers

Aberrant RNA modifications are frequently linked to chemotherapy resistance by altering gene expression and signaling pathways in genitourinary system cancers, including breast, ovarian, cervical, prostate, and bladder cancers. In breast cancer, METTL3 enhances ADR resistance by methylating EGF mRNA, which increases homologous recombination (HR) repair efficiency and reduces DNA damage. In ovarian cancer, elevated ALKBH5 levels increase cisplatin resistance by demethylating HOXA10, thereby promoting cell proliferation. Cervical cancer shows increased CENPK expression via ZC3H13-mediated mRNA methylation, which enhances stemness and drug resistance. Conversely, in bladder cancer, downregulation of ALKBH5 is associated with improved cisplatin sensitivity due to reduced CK2 α -mediated glycolysis. Targeting RNA methylation pathways thus presents a promising strategy for overcoming drug resistance in genitourinary system cancers

Effects of abnormal RNA modifications on chemotherapy resistance in respiratory system cancers and other cancers

Recent studies have elucidated the impact of aberrant RNA modifications on chemotherapy resistance in respiratory system cancers, such as lung cancer (LC). In small-cell lung cancer (SCLC), elevated METTL3 levels induce chemoresistance by downregulating decapping protein 2 (DCP2) [313]. DCP2 suppression activates the Pink1–Parkin mitochondrial autophagy pathway, mitigating mitochondrial damage and conferring resistance to cisplatin and etoposide in H69 and H446 cells [259].

In nasopharyngeal carcinoma (NPC), increased METTL5/TRMT112 mediates m6A modification at position 1832 (m6A1832) in 18 S rRNA, essential for 80 S ribosome assembly and enhancing global mRNA translation [305]. METTL5 promotes the translation of heat shock transcription factor 4b (HSF4b), which subsequently activates heat shock protein 90 beta family member 1 (HSP90B1). HSP90B1 interacts with oncogenic mutant p53 (mutp53), inhibiting its ubiquitination, thereby promoting tumorigenesis and resistance to cisplatin and docetaxel in NPC [252]. METTL1 and its mediated m7G tRNA modification are also pivotal in NPC chemoresistance. METTL1/WDR4 upregulates the translation of mRNAs involved in the WNT/ β -catenin signaling pathway, promoting epithelial–mesenchymal transition (EMT) and enhancing resistance to cisplatin and docetaxel. Aryl hydrocarbon receptor nuclear

translocator (ARNT) acts as a negative regulator of METTL1, reducing its oncogenic potential in NPC [253].

In glioma, the Warburg effect stimulates exosomal circ_0072083 release, which upregulates ALKBH5 expression, enhancing NANOG mRNA demethylation and stability, thereby promoting Temozolomide (TMZ) resistance [336]. Additionally, the long non-coding RNA JPX interacts with FTO, boosting FTO-mediated demethylation of phosphoinositide-dependent kinase-1 (PDK1) mRNA. This interaction increases PDK1 expression, further promoting aerobic glycolysis and TMZ resistance in glioma [337]. In osteosarcoma, overexpressed METTL1/WDR4 enhances m7G tRNA modification and the translation of oncogenic lysyl oxidase-like 2 (LOXL2), facilitating tumor progression and ADR resistance [254]. Moreover, the interplay between DNA cytosine methylation and m5C modification affects chemotherapy-induced apoptosis in osteosarcoma. DNA methyltransferase I (DNMT1) suppresses NSUN2 expression and subsequent m5C modification on both DNA promoters and mRNAs of anti-apoptotic target genes AXL, NOTCH2, and YAP1, inducing apoptosis in osteosarcoma cells treated with cisplatin or ADR [255].

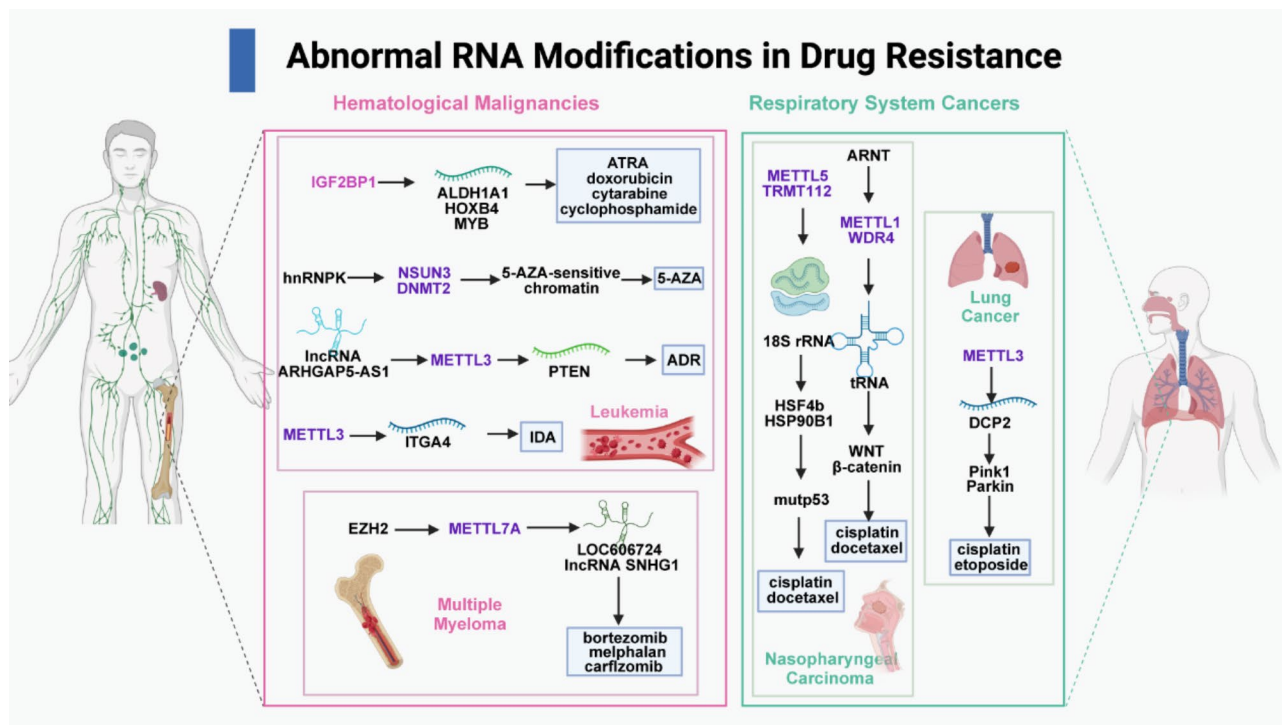


Fig. 6 Mechanisms of abnormal RNA modifications involved in chemotherapy resistance in hematologic malignancies and respiratory system cancers. Abnormal RNA methylation plays a significant role in chemotherapy resistance across various cancers. In leukemia, IGF2BP1 enhances resistance by regulating genes such as HOXB4 and MYB, impacting responses to treatments like ATRA and doxorubicin. METTL3 further contributes to resistance through m6A methylation of ITGA4, affecting homing and engraftment. Additionally, LINC00470 decreases PTEN expression *via* METTL3, activating AKT signaling and increasing resistance to ADR. In multiple myeloma, elevated METTL7A levels promote chemotherapy evasion by enhancing exosomal mechanisms. In lung cancer and nasopharyngeal carcinoma, higher levels of METTL3 and METTL5 lead to chemoresistance by activating mitochondrial autophagy and enhancing the translation of oncogenic factors, respectively. These findings underscore the complex role of RNA modifications in treatment resistance, highlighting the urgent need for targeted therapeutic strategies

Role of abnormal RNA modifications in resistance to other Anti-cancer therapies

Role of abnormal RNA modifications in resistance to targeted therapy

Sorafenib, the first FDA-approved drug for advanced hepatocellular carcinoma (HCC), faces limited efficacy due to resistance development. Hepatocyte nuclear factor 3-gamma (HNF3 γ), a regulator of hepatocyte and liver cancer stem cell differentiation, is pivotal in sorafenib resistance. Recent research indicates that METTL14 reduces HNF3 γ mRNA expression *via* m6A modification. Lower HNF3 γ levels hinder the activation of organic anion-transporting polypeptides 1B1 (OATP1B1) and 1B3 (OATP1B3), which are essential for drug uptake. Consequently, reduced HNF3 γ diminishes HCC cells' sensitivity to sorafenib's growth-inhibiting and proapoptotic effects, undermining its therapeutic efficacy [232]. Forkhead box O3 (FOXO3)-mediated autophagy contributes to sorafenib resistance in HCC. Under hypoxia, METTL3 depletion suppresses m6A modification of FOXO3 mRNA through a YTHDF1-dependent mechanism, leading to decreased FOXO3 expression. Reduced FOXO3 enhances angiogenesis and autophagic

flux, promoting sorafenib resistance and tumor growth in HCC [233]. Lenvatinib-resistant HCC tissues exhibit increased m7G modification levels and upregulated METTL1 and WDR4, correlating with poor clinical outcomes [164, 234]. WDR4 enhances TRIM28 translation, increasing stemness and lenvatinib resistance in HCC cells. Leukemia, a severe malignancy, often involves activating receptor tyrosine kinase (RTK) mutations, making tyrosine kinase inhibitors (TKIs) like erlotinib and imatinib essential treatments. The m6A modification plays a pivotal role in TKI resistance development in leukemia. The FTO–m6A axis has emerged as a novel biomarker for TKI resistance. Overexpression of FTO and reduced m6A modification levels are associated with genetically homogeneous leukemia cells harboring BCR/ABL, KIT, or FLT3 mutations. Thus, targeting the FTO–m6A axis offers a promising strategy to overcome TKI resistance in leukemia [256]. Crizotinib, a TKI targeting c-MET/ALK/ROS1, is an FDA-approved first-line treatment for NSCLC with ALK mutations, ROS1 rearrangement, or c-MET overactivation. Recent studies suggest that the histone deacetylase inhibitor chidamide enhances crizotinib's effectiveness in ALK mutant-negative NSCLC cell

lines, particularly those with high c-MET expression. In HCC827 and H661 NSCLC cells, chidamide downregulates METTL3 and WTAP, inhibiting c-MET mRNA modification and increasing NSCLC cells' sensitivity to crizotinib, thereby inhibiting cell growth [257]. Furthermore, METTL3-mediated autophagy counters the autophagy suppression induced by the anticancer drug β -elemene, thereby enhancing gefitinib resistance in NSCLC [258]. m5C hypermethylation and NSUN2 are linked to intrinsic gefitinib resistance and tumor recurrence in EGFR-mutant NSCLC. Overexpressed NSUN2 interacts with YBX1, boosting the translation of quiescine sulfhydryl oxidase 1 (QSOX1) mRNA, thus enhancing the proliferative and colony-forming capabilities of gefitinib-resistant NSCLC cells [260]. Another mechanism underlying TKI resistance in NSCLC involves the upregulation of the hepatocyte growth factor receptor MET. Increased A-to-I editing of miR-411-5p directly decreases MET protein expression and reduces downstream ERK signaling activity, thereby sensitizing NSCLC cells to gefitinib and Osimertinib [261]. In PC9 and A549 lung adenocarcinoma (LUAD) cells, METTL3 stabilizes the lncRNA SNHG17, leading to its upregulation. Elevated SNHG17 facilitates the epigenetic suppression of large tumor suppressor kinase 2 (LATS2) *via* interaction with EZH2, promoting gefitinib resistance, cell migration, invasion, and EMT [262]. METTL3, along with YTHDF2, promotes miR-146a expression while suppressing TUSC7 expression in an m6A-dependent manner, maintaining active Notch signaling and exacerbating erlotinib resistance in LUAD [263]. METTL7B increases the levels of three key ROS scavengers—glutathione peroxidase 4 (GPX4), superoxide dismutase 1 (SOD1), and heme oxygenase 1 (HMOX1)—in PC9 and HCC827 LUAD cells, thereby inducing glutathione metabolism and enhancing resistance to gefitinib and Osimertinib [264]. In A375R melanoma cells, METTL3 enhances the m6A modification of EGFR mRNA, significantly improving its translation efficiency. Upregulated EGFR activates the RAF/MEK/ERK signaling pathway, contributing to resistance against the BRAF (V600E) kinase inhibitor PLX4032 in melanoma [265].

Role of abnormal RNA modifications in resistance to immunotherapy

Despite the abundance of neoantigens in patients, tumor-associated antigens are essential for eliciting spontaneous anti-tumor immune responses. Research indicates that RNA modification regulators significantly influence the response to immune checkpoint blockade (Fig. 7). Most studies on m6A modification related to resistance to immune checkpoint inhibitors have concentrated on PD-1/PD-L1 inhibitors. In melanoma, YTHDF1 specifically recognizes m6A-modified mRNAs encoding

lysosomal proteases, enhancing their translation in dendritic cells. This mechanism limits tumor antigen cross-presentation and impairs the cross-priming of CD8+T cells' anti-tumor responses during anti-PD-1 immunotherapy [266]. Under metabolic stress, melanoma cells elevate FTO levels *via* autophagy and NF- κ B signaling, leading to resistance to interferon-gamma (IFN- γ) and anti-PD-1 treatment. FTO knockdown increases the RNA decay of intrinsic pro-tumorigenic genes, including PD-1, CXCR4, and SOX10, through YTHDF2 in melanoma cells [267]. In colorectal cancer (CRC), METTL3 and METTL14 negatively impact genes involved in IFN- γ and IFN- β pathways, such as STAT1 and IRF1, reducing cytotoxic CD8+T cell infiltration and diminishing the response to anti-PD-1 immunotherapy, especially in mismatch repair-proficient or low microsatellite instability CRC cases [227]. Furthermore, glucose directly activates NSUN2, stabilizing three prime repair exonuclease 2 (TREX2) mRNA and suppressing cGAS/stimulator of interferon genes (STING) signaling. This cGAS/STING axis drives resistance in immunologically "cold" tumors to anti-PD-1 immunotherapy and promotes tumorigenesis [268]. Recent studies have underscored that A-to-I editing affects therapeutic responses in cancer by generating RNA editing events linked to drug resistance [338, 339]. In PDAC, often classified as an immunologically "cold" tumor, elevated METTL3 enhances anti-tumor immunity by blocking A-to-I editing of m6A-modified transcripts and promoting endogenous dsRNA accumulation. dsRNA stress activates RLRs, triggering signaling cascades that amplify the anti-tumor immune response [223].

Optimizing Treatment Efficacy Through the Combination of Traditional Anti-cancer Drugs and Modulation of RNA Modifications

Recent research advancements underscore the pivotal role of RNA modifications in fostering therapeutic resistance in cancer, paving the way for innovative strategies to enhance the effectiveness of conventional anti-cancer treatments. One promising method focuses on inhibiting the enzymatic activity or expression of proteins associated with RNA modification [340]. This approach includes the deployment of small molecule inhibitors, such as the extensively studied FTO inhibitors Rhein, R-2-hydroxyglutarate (R-2HG), meclofenamic acid (MA), FB23, and FB23-2 [101, 341–345]. Notably, the combination of Rhein with TKIs exhibits synergistic effects, effectively targeting TKI-resistant leukemia cells, including those from patients with relapsed or refractory leukemia [256]. Additionally, Rhein significantly enhances the antiproliferative impact of the anti-PD-L1 antibody atezolizumab in 4T1 BC xenografts by augmenting the proportion of CD8+T cells in the spleen and tumor

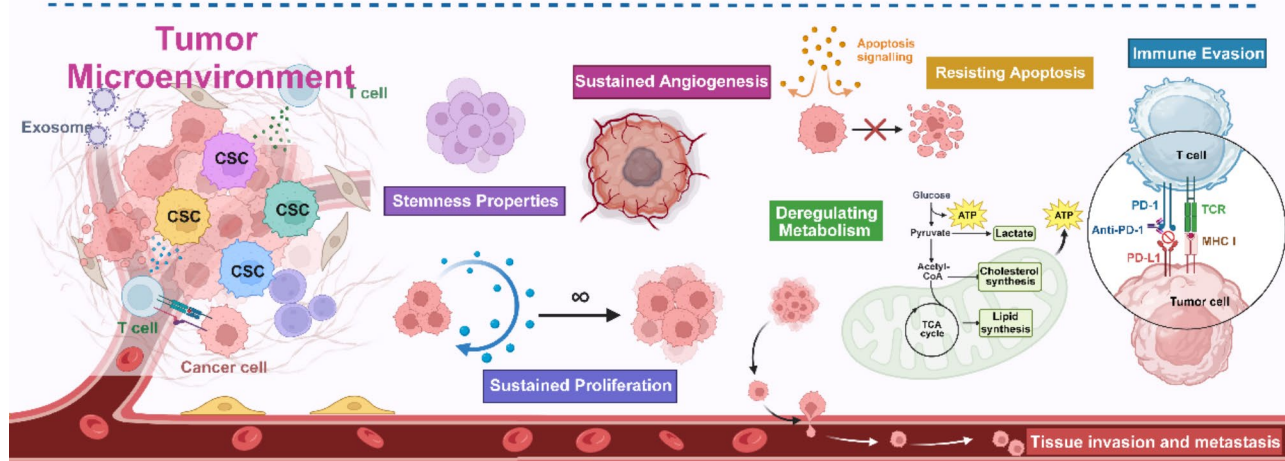
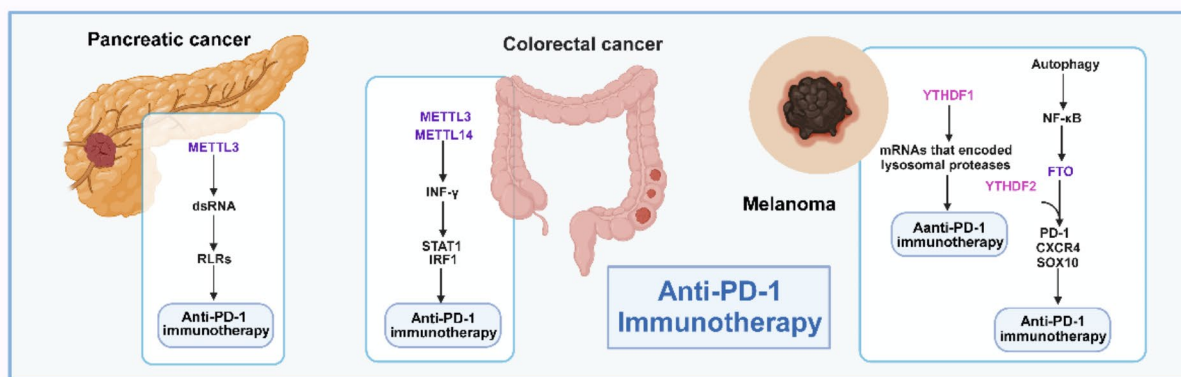
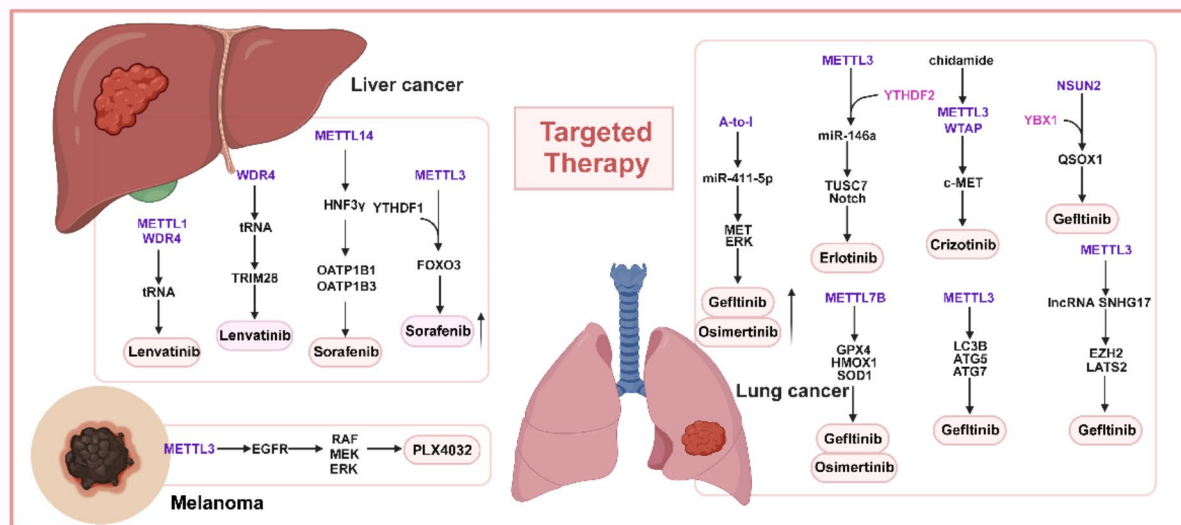


Fig. 7 Mechanisms of abnormal RNA modifications involved in resistance to targeted therapy and immunotherapy in cancer. Beyond contributing to chemotherapy resistance, abnormal RNA modifications can diminish the efficacy of targeted therapies and immunotherapies, resulting in treatment failure or cancer recurrence. Modifications such as m6A, m7G, m5C, and A-to-I editing promote resistance to tyrosine kinase inhibitors in various cancers, including hepatocellular carcinoma, leukemia, and lung cancer. For example, METTL3 reduces the therapeutic efficacy of the BRAF inhibitor PLX4032 in melanoma by activating the epidermal growth factor receptor (EGFR) pathway. Additionally, RNA modifications can disrupt gene expression and intracellular signaling pathways, leading to abnormal expression of immune checkpoints, interference with antigen presentation and recognition, suppression of cytotoxic T-cell infiltration, and the development of immunotherapy resistance

tissues and elevating apoptotic factors in BC tissues [346]. Another direct FTO inhibitor, Saikosaponin-d (SsD), displays broad anti-proliferative effects in leukemia and improves TKI resistance mediated by FTO [347]. Moreover, R-2HG, in conjunction with first-line chemotherapeutic drugs such as ATRA, AZA, decitabine, and ADR, synergistically induces cell cycle arrest and apoptosis in leukemia and glioma cells, underscoring the efficacy of targeting RNA modification regulators in cancer treatment strategies [342]. The FTO inhibitor 18,097 has been shown to suppress cell growth and lung colonization in BC animal studies, while FB23-2 demonstrates therapeutic potential for clear cell renal cell carcinoma (ccRCC) by inhibiting tumor growth and prolonging survival in PDX model mice [348, 349].

Inhibitors targeting other RNA modification-related enzymes also exhibit therapeutic potential across various cancer types. For instance, ALK-04, a small-molecule inhibitor of ALKBH5, enhances the efficacy of anti-PD-1 immunotherapy in melanoma by modifying the TME [350]. TAS0612, targeting the m5C reader YBX1, reduces antiestrogen resistance in patients with triple-negative BC [351]. Targeting METTL3 presents considerable promise in overcoming cancer drug resistance [352, 353]. A significant development is STM2457, a highly potent and selective catalytic inhibitor of METTL3, which shows potential against AML by targeting key stem cell subpopulations, leading to diminished AML growth, improved differentiation, and increased apoptosis [354]. STM2457 effectively reverses homing/engraftment and drug resistance in IDA-resistant AML cells, contributing to decreased proliferation and increased apoptosis [247, 289, 352, 355]. In primary resistant HCC cell line MHCC97H and acquired resistant Huh7-LR cells, as well as multiple mouse HCC models, STM2457 enhances tumor response to lenvatinib and alleviates gemcitabine resistance in intrahepatic cholangiocarcinoma (ICC) by inhibiting glycolytic reprogramming [216, 281]. In SHH subgroup medulloblastoma (SHH-MB), targeting METTL3 with STM2457 represses Sonic hedgehog signaling, thereby restraining tumor progression [356]. WD6305, a PROTAC degrader of the METTL3-METTL14 complex, exhibits more effective anti-leukemic effects than its parent inhibitor by suppressing m6A modification and affecting various signaling pathways involved in AML development and proliferation [357]. Additionally, a designed stapled peptide inhibitor (RSM3) targeting the METTL3-METTL14 binding interface and inhibiting global RNA methylation significantly suppresses tumor growth in diverse cancer types, particularly in prostate cancer (PCa) cell lines [358].

Increasing evidence underscores the pivotal role of RNA modifications in cancer immunotherapy, significantly enhancing the efficacy of immune checkpoint

blockade (ICB) and chimeric antigen receptor (CAR) T-cell therapy. RNA modifications achieve this by directly suppressing tumor growth, modulating immune cell activation, and promoting immune cell infiltration into the TME [359]. A Phase I clinical trial is currently evaluating the anti-tumor efficacy of the METTL3 inhibitor STC-15, both as a monotherapy and in combination with an anti-PD-1 antibody for treating solid tumors. In various pre-clinical cancer models, STC-15 activates innate immune pathways and enhances CD8+T cell-mediated tumor cell death. It also amplifies the anti-tumor effects of anti-PD-1 therapy, generating a durable anti-tumor immune response, indicating significant potential for METTL3 inhibition in cancer treatment [360]. In non-alcoholic fatty liver disease-associated HCC (NAFLD-HCC), the combination of STM2457 and ICB therapy dramatically boosts the cytotoxic CD8+T cell-mediated antitumor response and overcomes anti-PD-1 resistance, leading to a synergistic suppression of NAFLD-HCC. In NSCLC, STM2457 upregulates PD-L1 expression, thereby improving immunotherapy outcomes both in vivo and in vitro [361]. While small molecule inhibitors can be rapidly developed and tested in clinical trials, offering a scalable and cost-effective treatment strategy, their application is restricted by potential off-target effects, the development of resistance over time, and limited bio-availability and stability [27, 362, 363].

In addition to small molecule inhibitors targeting RNA modification regulators, advanced techniques such as CRISPR/Cas9, RNA interference (RNAi), and nanomedicine-based technology provide further methods to target and suppress these regulators [316, 364–367]. The CRISPR/Cas9 system, in particular, offers significant potential for enhancing drug sensitivity and enabling personalized therapies in cancer treatment [368–370]. For instance, METTL3 knockdown *via* CRISPR/Cas9 in head and neck squamous cell carcinoma has been shown to increase cancer cell sensitivity to cisplatin [371]. A novel approach by Liu et al. involved developing a programmable RNA m6A editing system by fusing CRISPR/Cas9 with a single-chain m6A methyltransferase, allowing site-specific methylation in different mRNA regions using guide RNA [372]. Additionally, CRISPR/Cas9 fused with ALKBH5 or FTO, m6A ‘erasers,’ can achieve site-specific RNA demethylation. The increasing versatility of CRISPR/Cas enzymes suggests the potential for creating m6A editors with smaller sizes, higher specificity, and adjustable features, enabling precise m6A modifications on RNA without altering the primary sequence. The high efficiency and precision of the CRISPR/Cas9 technique make it a valuable tool for exploring drug targets [373–375]. For example, genome-wide CRISPR/Cas9 knockout screening across over 800 cancer cell lines revealed a stronger dependency on METTL16 in

leukemias compared to other cancer types, particularly in AML cell lines [376]. Despite these advancements, CRISPR/Cas9-based RNA modifications face limitations, including unstable genome editing efficiency and specificity, off-target effects, and the induction of immune responses [368]. While the CRISPR/Cas9 system boasts high efficiency, the safe and effective delivery of CRISPR components to target cells is crucial for achieving high-efficiency gene editing [377]. The choice and optimization of delivery systems are key factors; viral vectors offer high transfection efficiency but pose safety concerns such as oncogenicity, insertional mutagenesis, and immunogenicity. Off-target effects also reduce the specificity of CRISPR/Cas9 gene editing [378–380]. Furthermore, nanomedicine-based RNA modification has greatly expanded, improving drug bioavailability, tumor targeting, and intracellular release efficiency, thus enhancing therapeutic outcomes while mitigating adverse effects [381–386]. An innovative application of nanotechnology in cancer therapy involves utilizing nanoparticles engineered to deliver mRNA or small interfering RNA (siRNA) targeting RNA modification-related regulators, effectively remodeling the TME and achieving anti-cancer effects [355, 367, 387, 388]. For example, a PLGA-based nanoplatform loaded with LINC00958 siRNA significantly decreased the proliferative ability of HCC cells and reduced xenograft tumor growth by inhibiting m6A-mediated upregulation of LINC00958, demonstrating the potential of targeted nanomedicine strategies in controlling tumor progression [389]. Additionally, combining an antigen-capturing nanoplatform designed for co-delivering tumor-associated antigens (TAAs) and FTO into tumor-infiltrating dendritic cells (TIDCs) with thermal ablation significantly enhanced DC maturation and triggered tumor infiltration of effector T cells, thereby boosting the anti-tumor effects of ICB treatment in HCC [390]. Moreover, using a Toll-like receptor 9 agonist-conjugated siRNA to selectively target YTHDF2 in tumor-associated macrophages (TAMs) reprogrammed TAMs towards an anti-tumoral phenotype, increasing their antigen cross-presentation capabilities and improving CD8⁺T cell-mediated antitumor immunity. This reprogramming not only restrained tumor growth but also significantly boosted the efficacy of PD-L1 antibody therapy [391]. However, challenges such as the complexity of nanoparticle design and manufacturing, long-term safety, potential toxicity, and off-target effects hinder the clinical reliability of nanotechnology applications [392–394].

The investigation of RNA modification mechanisms in drug resistance provides a promising route for developing innovative therapeutic strategies to combat cancer resistance. Nonetheless, the field of translational drug discovery targeting RNA modifications is nascent, with

no clinical trials yet employing m6A inhibitors for cancer treatment [395–397]. The global effects of methylation and demethylation induced by RNA modification inhibitors or activators demand thorough investigation due to their extensive distribution across nearly all RNA species and significant biological implications. RNA modifications display cellular heterogeneity, meaning the same writer, eraser, and reader proteins may function differently across various cellular contexts. Additionally, the impact of m6A modifications varies depending on their location within different regions of the same RNA. This complex landscape necessitates precise targeting and modulation of RNA modifications to maximize therapeutic efficacy while minimizing potential adverse effects [176, 256, 335, 398, 399]. Future clinical trials must explore the synergistic anti-cancer effects of combining traditional anti-cancer drugs with RNA modification inhibitors, potentially paving new pathways for effectively treating resistant cancers.

Conclusions and outlooks

Recent advancements in epigenetic research have highlighted the pivotal role of RNA modifications in tumorigenesis and drug resistance. Modifications such as m6A, m1A, m5C, m7G, Ψ, and A-to-I editing significantly influence gene expression by affecting RNA splicing, stability, translation, and degradation, thereby impacting the function and malignancy of tumor cells. Many RNA modification regulators are overexpressed in cancer cells, contributing to enhanced proliferation, stemness, and resistance to conventional therapies, leading to poor prognosis and high recurrence rates in most cancers.

The dysregulation of RNA modification regulators and their downstream pathways is linked to various mechanisms of therapeutic resistance, including altered drug targets, disrupted drug efflux, and evasion of drug-induced apoptosis. Emerging studies reveal both oncogenic and tumor-suppressive roles of these regulators in different cancers. For example, METTL3 functions as an oncogene in multiple cancer types, enhancing drug resistance through various signaling pathways, yet it also potentially improves the therapeutic efficacy of sorafenib in HCC. These dual roles underscore the complexity of RNA modifications and necessitate further investigation into their specific functions in different tumor contexts to develop effective treatments.

Research on RNA modification inhibitors, particularly those targeting m6A, is gaining traction as a novel strategy to overcome cancer drug resistance. However, specific drugs targeting other RNA modifications, such as m1A, m5C, and m7G, remain scarce due to the intricate mechanisms involved and the limited understanding of their roles and quantification in cancer. Consequently, developing precise methods for detecting RNA

modifications and identifying key modified RNAs in resistant cancers is imperative.

Despite the therapeutic potential of RNA modification inhibitors, drug development in this area is still in its infancy, with only a few candidates undergoing clinical testing. This gap highlights both a challenge and a significant opportunity for therapeutic innovation. Expanding research to include a broader array of RNA modifications could yield more therapeutic options. Combining RNA modification inhibitors with traditional anti-cancer therapies is a promising strategy for enhancing treatment efficacy and achieving synergistic anti-tumor effects. Developing targeted therapies that modulate RNA modifications without disrupting the overall epigenetic landscape could significantly advance cancer treatment. To fully harness the therapeutic potential of RNA modification inhibitors, a comprehensive investigation into the complex interplay among various RNA modifications and their interactions within the TME is essential. Large-scale clinical trials are necessary to validate the efficacy and safety of RNA modification-based anti-cancer therapies.

In conclusion, RNA modifications offer promising avenues for improving cancer treatment efficacy. Understanding how these modifications influence tumor cell responses to drugs may guide the development of novel cancer treatments and facilitate the design of individualized therapies tailored to the unique epigenetic profiles of individual cancers.

Abbreviations

m6A	N6-methyladenosine
m1A	N1-methyladenosine
m5C	5-methylcytosine
m7G	7-methylguanosine
Ψ	Pseudouridine
A-to-I editing	Adenosine-to-inosine editing
TME	Tumor microenvironment
EMT	Epithelial–mesenchymal transition
mRNAs	messenger RNAs
lncRNAs	long non-coding RNAs
rRNAs	ribosomal RNAs
tRNAs	transfer RNAs
miRNAs	microRNAs
dsRNAs	double-stranded RNAs
ceRNA	endogenous RNA
circRNAs	circular RNAs
DDR	DNA damage repair
PC	Pancreatic cancer
CRC	Colorectal cancer
GC	Gastric cancer
BC	Breast cancer
OC	Ovarian cancer
BCa	Bladder cancer
CRPC	Castration-resistant prostate cancer
CSPC	Castration-sensitive prostate cancer
MDS	Myelodysplastic syndrome
AML	Acute myeloid leukemia
CML	Chronic myeloid leukemia
MM	Multiple myeloma
NPC	Nasopharyngeal carcinoma
HCC	Hepatocellular carcinoma
LC	Lung cancer

NSCLC	Non-small cell lung cancer
SCLC	Small-cell lung cancer
CSCs	Cancer stem cells
5-FU	5-fluorouracil
TKIs	Tyrosine kinase inhibitors
METTL3	Methyltransferase-like 3
WTAP	Wilms tumor 1-associated protein
VIRMA	VIR-like m6A methyltransferase associated
RBM15	RNA-binding motif protein 15
ZC3H13	Zinc finger CCCH-type containing 13
FTO	Fat mass and obesity-associated protein
ALKBH5	AlkB homolog 5
YTHDF1	YTH N6-methyladenosine RNA binding protein 1
YTHDC1	YTH domain-containing protein 1
IGFBPs	Insulin-like growth factor 1 mRNA-binding proteins
MSI2	Musashi2
PRRC2A	Proline-rich coiled-coil containing protein 2 A
HNRNPA2B1	Heterogeneous nuclear ribonucleoprotein A2/B1
TRMT10	tRNA methyltransferase 10 homolog A
NSUN	NOL1/NOP2/SUN domain
DNMT2	DNA methyltransferase-like 2
TET	Ten-eleven translocation
ALYREF	Aly/REF export factor
YBX1	Y-box binding protein 1
FMRP	Fragile X mental retardation protein
WDR4	WD repeat domain 4
WBSCR22	Williams–Beuren syndrome chromosomal region 22
RNMT	RNA guanine-7 methyltransferase
RAM	RNMT-activating miniprotein
DKC1	Dyskerin pseudouridine synthase 1
TERC	Telomerase RNA component
ADARs	Adenosine deaminases acting on RNAs

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Author contributions

Chen Xue, Shaohua Li, Dongming Yan and Xuqiang Zhu designed the structure of the review. Di Chen, Xinyu Gu and Yeltai Nurzat, and Lixia Xu wrote the article. Xueyuan Li, Lixin Wu, and Henan Jiao draw the figures. Di Chen, Henan Jiao and Peng Gao completed the tables. Chen Xue, Shaohua Li, Dongming Yan, and Xuqiang Zhu helped with the final revision of the review. All authors reviewed the manuscript and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The corresponding author has obtained consent for publication.

Competing interests

The authors declare no competing interests.

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