Genes & Diseases (2023) 10, 135–150

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REVIEW ARTICLE

Dynamic m6A-ncRNAs association and their impact on cancer pathogenesis, immune regulation and therapeutic response

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Received 5 September 2021; received in revised form 11 October 2021; accepted 25 October 2021
Available online 10 November 2021

KEYWORDS
Cancer;
Immune regulation;
N-6-Methyladenosine;
Non-coding RNAs;
Therapeutic response

Abstract Several types of modifications have been proven to participate in the metabolism and processing of different RNA types, including non-coding RNAs (ncRNAs). N-6-methyladenosine (m6A) is a dynamic and reversible RNA modification that is closely involved in the ncRNA homeostasis, and serves as a crucial regulator for multiple cancer-associated signaling pathways. The ncRNAs usually regulate the epigenetic modification, mRNA transcription and other biological processes, displaying enormous roles in human cancers. In this review, we summarized the significant implications of m6A-ncRNA interaction in various types of cancers. In particular, the interplay between m6A and ncRNAs in cancer pathogenesis and therapeutic resistance are being widely recognized. We also discussed the relevance of m6A-ncRNA interaction in immune regulation, followed by the interference on cancer immunotherapeutic procedures. In addition, we briefly highlighted the computation tools that could identify the accurate features of m6A methylome among ncRNAs. In summary, this review would pave the way for a better understanding of the biological functions of m6A-ncRNA crosstalk in cancer research and treatment.

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Peer review under responsibility of Chongqing Medical University.
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https://doi.org/10.1016/j.gendis.2021.10.004

Introduction

Nowadays, more than 100 different types of chemical modifications have been identified in the ribose nucleic acid (RNA), including messenger RNAs (mRNAs) and non-coding RNAs (ncRNAs).[1,2] Amongst RNA modifications, N-6-methyladenosine (m6A) is the most prevalently and abundantly modified form present in RNA molecules. More importantly, m6A RNA modification have been proven to function as a promising regulatory layer that coordinate diverse aspects of RNA dynamics, such as RNA processing, translational efficiency and degradation.[3] In recent years, a growing number of explorations have demonstrated the important biological significance of m6A epitranscriptome in cancer pathogenesis and highlighted the potential values of m6A regulators in therapeutic response and prognosis.

The ncRNAs, such as micro-RNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), have been revealed to regulate cell growth and development *in vitro* and *in vivo*, further contributing to many hallmarks of disease phenotypes, including cancers.[4–6] Mounting evidence has demonstrated that the interactions between m6A modification and ncRNAs are extremely widespread.[7] As the most prominent RNA modification, m6A is closely involved in ncRNA homeostasis, and serves as a crucial regulator participating in many physiological and pathological processes. Identification of m6A regulators have reported that m6A modification is critical throughout the whole ncRNA life cycle, such as miRNA biogenesis, lncRNA processing, and circRNA functions.[8,9] More importantly, m6A modification affects the ncRNA-RNA and ncRNA-protein interactions that regulate and control their specific molecular functions, which is involved in cancer pathogenesis and therapeutic response.[10]

This review mainly provides an overview of m6A-ncRNA association in malignant progression, and discuss the recent reports that have provided novel insights into the underlying regulatory mechanisms of the m6A-ncRNA axis for therapy response. In addition, we also pointed some promising areas for future explorations, which might influence the potential clinical implications, specifically like the impact of m6A-ncRNA interaction on immune regulation. Evaluating the detailed molecular mechanisms and associated signaling pathways will help strengthen our understanding of m6A-ncRNA axis in cancer pathogenesis, offering promising therapeutic targets to improve the efficacy of cancer treatment.

Modulation of m6A methylation and demethylation

M6A modification, which was first discovered in the 1970s, has been confirmed to play extremely important functions in many biological processes through modulating the ncRNA metabolism and processing.[11,12] Moreover, emerging findings have implicated the essential regulators underlying the biological importance of m6A methylome in cancers[13–15] (Fig. 1). The canonical m6A motif is preferentially identified in a consensus sequence, consisting of RRACH (where R represents A or G, and H represents A, U or C).[16] Several bioinformatic tools, such as m6Aboost[17] and DeepPromise,[18] have been developed to search for and discover the RRACH motif surrounding m6A methylation sites.

M6A modification is likely to be facilitated by the functional interaction between RNA methyltransferases and demethylases. As a dynamic reversible biological process, m6A modification is mainly catalyzed by a methyltransferase-like complex (MTC) consisting of at least three core subunits, methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14) and Wilms' tumor 1-associating protein (WTAP).[19] In MTC complex, METTL3 is the catalytic subunit, while METTL14 functions as an RNA-binding platform.[20,21] Serving as the primarily m6A writers, METTL3-METTL14-WTAP complex catalyzes the addition of a methyl group to the N6-position of adenine in the substrate RNA molecules, therefore producing RNA N6-adenosine methylation and effectively adding the m6A modification to mRNAs and ncRNAs.[22] In addition, other MTC subunits, such as METTL16,[23] VIRMA,[24] HAKAI,[13] RNA binding motif protein 15/15B (RBM15/15B)[25] and zinc finger CCCH-type containing 13 (ZC3H13),[26] have been recently identified as novel m6A writers that regulate multiple signaling pathways in m6A dependent manners, contributing to cancer progression.

The identification of m6A demethylases, AlkB homolog 5 (ALKBH5) and fat mass and obesity-associated protein (FTO), have confirmed that the m6A modification can be reversibly demethylated.[27] As m6A erasers, ALKBH5 and FTO could effectively reverse the m6A marks in substrates[28] and may play important roles. For example, RNA demethylation by ALKBH5 or FTO alters the stability and transactivity of *UDP-glucuronosyltransferases B7 (UGT2B7)* mRNA.[29] Two potent small-molecule FTO inhibitors, CS1 and CS2, have been demonstrated to exhibit strong antitumor effects in multiple types of cancers.[30] The meclofenamic acid (MA), another highly selective FTO inhibitor, could dramatically increase the cellular level of m6A in cervical cancer HeLa cells and suppress the cell growth.[31] Recently, Huang and colleagues used the structure-based rational design to identify the compounds FB23 and FB23-2 as two promising FTO inhibitors.[32] Mechanistically, FB23 and FB23-2 could inhibit the m6A demethylase activity of FTO by directly binding to FTO, leading to the suppression of proliferation and induction of apoptosis in human acute myeloid leukemia cells.[32] However, the potential tumor-suppressing effect of FTO inhibitors have not been confirmed in the clinical trials.[33] Therefore, it is of great

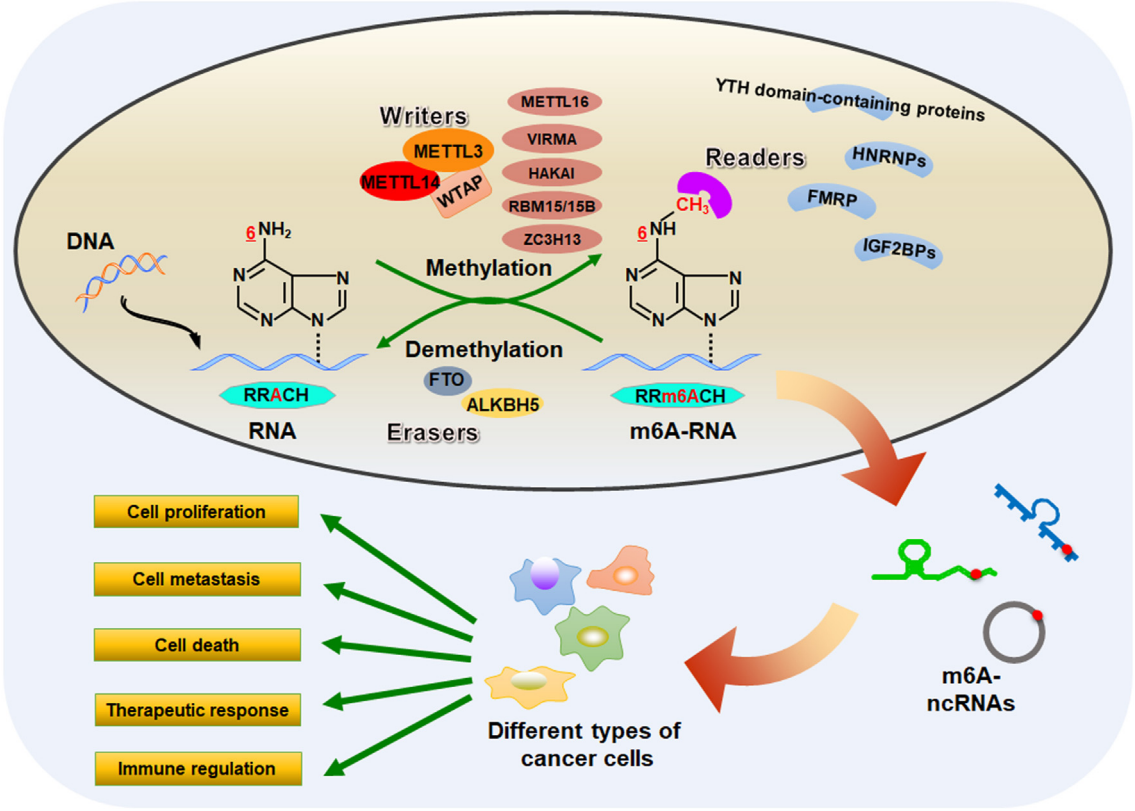

Figure 1 Reversible m6A modification on ncRNAs. Schematic representation of known regulatory components of m6A modification in ncRNAs. The m6A modification is mainly facilitated by the functional association between RNA methyltransferases and demethylases. Meanwhile, the m6A modified sites can also be recognized by a group of specific RNA-binding proteins. These m6A regulatory proteins play a predominant role in executing m6A functions on ncRNA metabolism in cancer biology.

importance to explore the clinical significance of these inhibitors for cancer therapy in the future. In addition, given that 9 homologs of AlkB protein, including ALKBH1-8 and FTO, have been discovered to date,[34] additional explorations are warranted to understand the underlying roles of all AlkB family members in m6A demethylation.

The m6A modified sites can also be recognized by a group of specific RNA-binding proteins, including YT521-B homology (YTH) domain-containing proteins, eukaryotic initiation factor (eIF), heterogeneous nuclear ribonucleoproteins (HNRNPs), fragile X mental retardation protein (FMRP) and insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs).[35,36] These m6A reader proteins play a predominant role in executing m6A functions on RNA metabolism. It has been documented that the dysregulation of m6A reader proteins also participate in a variety of biological processes.[37,38] Therefore, determine the underlying mechanisms of m6A regulators would be of great significance to elucidate their specific functions in RNA metabolism.

Crosstalk between M6A and noncoding RNAs in cancer pathogenesis

M6A methylation has multiple implications in regulating the ncRNA homeostasis. Aberrant regulatory machinery of m6A—ncRNA interaction have been associated with the pathophysiology of numerous diseases, especially cancers (Fig. 2). For example, METTL3 increased m6A level of lncRNA PCAT6, contributing to tumor growth and bone metastasis in prostate cancer.[39] YTHDF2-mediated m6A-dependent lncAY stability facilitated HCC progression.[40] FTO expression inversely correlated with miR-1266 during colorectal cancer progression.[41] However, the biological significance of m6A-ncRNA interactions and the corresponding regulatory mechanisms in cancer pathogenesis and treatment remain incompletely understood.

Impact of m6A on miRNA biogenesis and function

The miRNAs are the evolutionarily conserved small ncRNAs with a length of ~23 nucleotides and play functional roles in diverse biological behaviors in cancers, including cell proliferation and stress response.[42—44]

The first step of miRNA biogenesis is the processing of longer precursors of miRNAs (pre-miRNAs) in the nucleus by the DROSHA microprocessor complex, composed of the RNase III endonuclease DROSHA and a cofactor DiGeorge syndrome critical region 8 (DGCR8).[45,46] Increasingly, studies have established the biological function of m6A in promoting miRNA biogenesis. The m6A motif RRACH was over-represented in pre-miRNAs, and a single m6A site sufficiently drove pre-miRNA processing.[47] Consistent with the viewpoint that site-specific m6A is associated with pre-

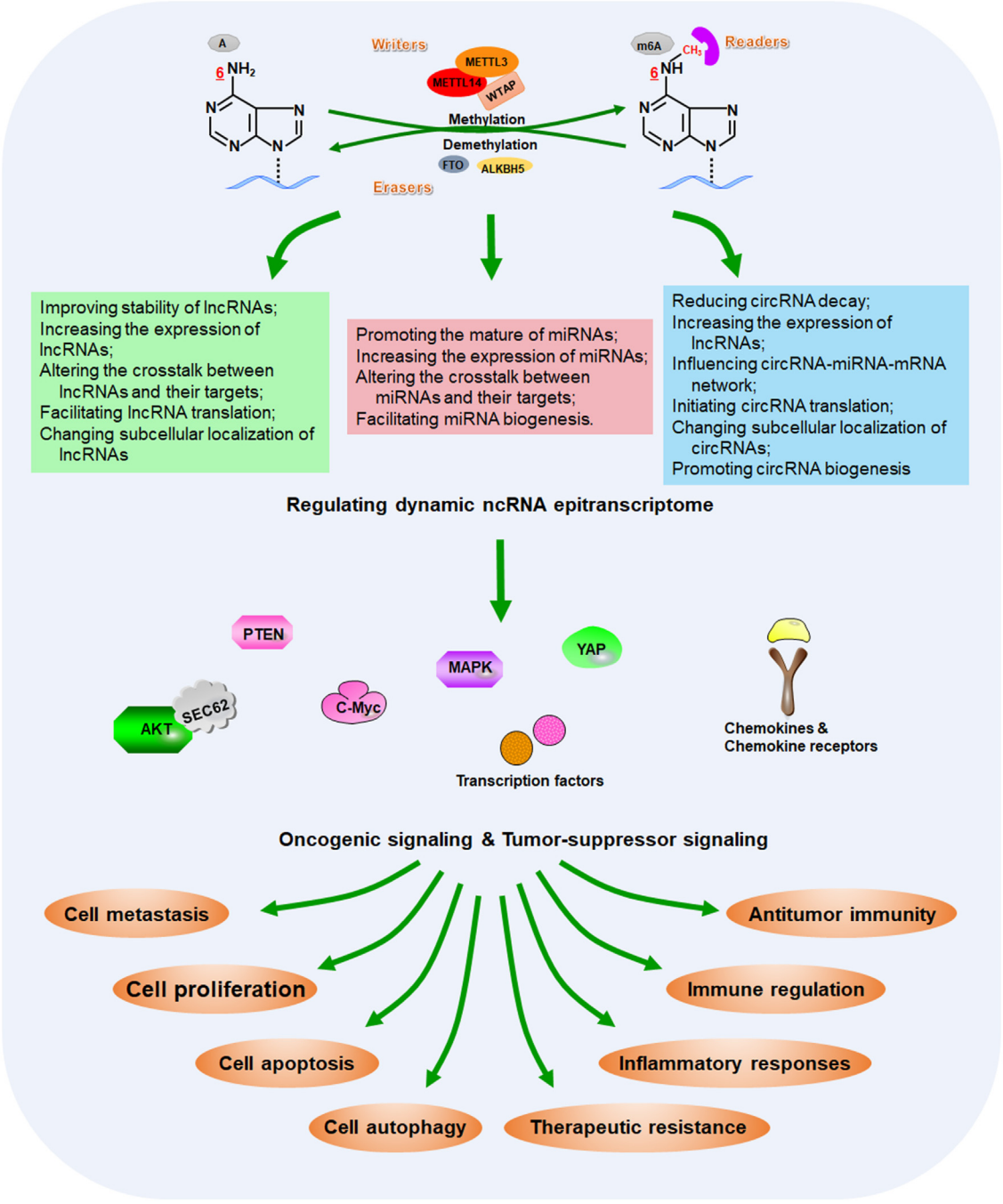

Figure 2 Multiple functions of m6A modifications on ncRNAs in the control of cancer pathogenesis and treatment. As the most prevalently and abundantly modified form, m6A RNA modification have been proven to function as a promising regulatory layer that coordinate multiple steps of ncRNA homeostasis, such as ncRNA stability, ncRNA—target interaction and subcellular localization. Aberrant m6A—ncRNA machinery could result in dysregulation of cancer-associated signaling pathways, which is involved in a variety of biological behaviors in cancers, especially like cancer development, immune regulation and therapeutic response.

miRNA methylation, two independent research groups demonstrated that m6A "reader" METTL3 enhanced the binding of DGCR8 to pre-miR-221/222 and pre-miR-92b, and positively regulated their mature forms, which concomitantly resulted in PTEN downregulation and pro-tumorigenic effects in bladder cancers[48] and gallbladder cancers.[49] In hepatocellular carcinoma (HCC), METTL3 overexpression triggered the malignant phenotypes of cancer cells by interacting with DGCR8 and positively modulating mature miR-873-5p. METTL3 was reported to promote the expression of miR-873-5p by increasing m6A abundance on pre-miR-873-5p in cells.[50] In addition, METTL14 suppressed the metastasis capability of HCC cells through interaction with DGCR8.[51] Mechanistically, decreased METTL14 negatively modulated the DGCR8 binding to pre-miR-126 in a m6A-dependent mechanism,

and led to pre-miRNA accumulation and miR-126 downregulation. Consequently, the m6A status alters the cross talk between miRNAs and their target mRNAs. METTL3 was found to methylate pri-miR-1246, further promoting its maturation and downregulating its downstream target SPRED2 in the development of colorectal cancer (CRC).[52] Likewise, upon treatment with cigarette smoke condensate, hypomethylated METTL3 increased the progression rate of pre-miR-25 to its mature form, miR-25-3p, via m6A-dependent pre-miRNA processing, which provoked the activation of oncogenic AKT signaling and thereby induced malignant phenotypes of pancreatic cancer cells.[53] Additionally, the m6A induced cleavage of precursor miRNAs is impaired and subsequent miRNA biogenesis was reduced in cells when treated with the short interfering RNAs (siRNAs) specifically targeting RNA methyltransferase, ultimately weakening the metastatic propensities of lung cancer cells.[54,55] All these findings reveal that acting as an important post-transcriptional modification, the METTL3/14-catalytic m6A modification is required for efficient initiating of miRNA biogenesis in cancer pathogenesis.

The members of DEAD box RNA helicases, for example DDX17, can serve as the co-factor of miRNA microprocessor, enhancing miRNA biogenesis through m6A modifications.[56,57] Thus, it will be imperative to investigate the possible interaction between DEAD box RNA helicases and other regulatory proteins participating in m6A modifications of miRNAs. DDX3 interacted with m6A "eraser" ALKBH5 to demethylate certain miRNAs and ubiquitously regulated cell growth and proliferation,[58] indicating that DDX3 functions as a partner of ALKBH5 to regulate dynamic miRNA epitranscriptome.

Another study supports the role of nuclear ''reader'' HNRNPA2B1 as a possible mediator of m6A-dependent miRNA processing events.[59] In this study, HNRNPA2B1 was implicated as an adaptor to recruit the DROSHA microprocessor complex to pre-miRNAs, subsequently triggering their processing into mature miRNAs. Moreover, increased miRNA processing induced by HNRNPA2/B1 overexpression contributed to acquired resistance to tamoxifen and fulvestrant in breast cancer cells.[60] Hence, HNRNPA2B1-depend m6A modification likely influences miRNA processing.[61] However, this hypothesis needs to be proven using more systematic and large-scale studies.

Taken together, m6A-dependent control of miRNA expression and biosynthesis are linked to the development and progression of human cancers, and is associated with overall survival in cancer patients.[10] Nevertheless, given that the underlying knowledge of RNA methylation in miRNA regulation is still in its infancy, additional valuable evidence for m6A regulatory patterns on the biogenesis and functions of miRNAs are worth further investigations in future trials.

miRNAs regulate m6A on mRNAs

Interestingly, miRNAs also regulate m6A modification through a sequence pairing mechanism. Notably, several miRNAs have been reported to exert its function by targeting the mRNA of m6A regulators. The predominant catalytic enzyme of m6A methyltransferase systems, METTL3, is responsible for increased m6A methylations of some carcinogenic mRNAs related to malignant transformation and therapeutic resistance.[62,63] As described by Cai and colleague,[64] miRNA let-7g reduced the expression of *METTL3* mRNA by targeting its 3′-UTR. Hepatitis B X-interacting protein (HBXIP) upregulated *METTL3* by interrupting the let-7g—METTL3 interaction, ultimately driving the breast cancer aggressiveness. Meanwhile, miR-4429 exerted a suppressive role in gastric cancer (GC) cells through targeting METTL3 and disturbing m6A-associated stabilization of oncogenic *SEC62* mRNA.[65] Similarly, miR-33a attenuated cell proliferation by directly targeting the 3′-UTR of *METTL3* mRNA, and seemed like a promising therapeutic target in non-small-cell lung carcinoma.[66] miR-186 was another effective therapeutic and prognostic biomarker in hepatoblastoma that targeted and downregulated *METTL3* expression, which finally led to significant inhibition of aggressive cellular phenotype both *in vitro* and *in vivo*.[67] Thus, regulating miRNAs—METTL3 signaling axis may be a potential targeting strategy, which in turn impairs the oncogenesis and improves the therapeutic effect.

The cross talk between miRNAs and RNA m6A "reader" proteins has been recently validated, to affect the biological behavior of cancer cells. YTHDF2 served as a m6A "reader" and selectively bound to m6A sites to mediate mRNA decay.[68] Similarly, Yang et al found the negative correlation between miR-145 and *YTHDF2* in HCC tissues and cells, where miR-145 targeted the 3′-UTR of *YTHDF2* mRNA and strongly stabilized m6A-containing mRNA, ultimately decreasing the malignancy of HCC.[69] In a recent study, proteomic analysis revealed m6A "reader" HNRNPF as putative hsa-miR-139-5p targets in thyroid cancer. Exogenous expression of hsa-miR-139-5p drastically reduced *HNRNPF* mRNA abundance, and affected the splicing events related to MAPK and AKT signaling cascades.[70] In ovarian cancers, miR-744-5p directly downregulated mRNA and protein expressions of *HNRNPC* and activated the intrinsic apoptotic pathways. In addition, HNRNPC overexpression caused diminished miR-21 expression and AKT phosphorylation, further leading to the pro-apoptotic effects. Strikingly, these apoptosis-inducing effects can be obviously enhanced when cells received combination treatment of carboplatin and miR-744-5p.[71] Moreover, exosomal miRNAs may reduce the magnitude of FTO methylation, thereby epigenetically affecting FTO expression and FTO-dependent mRNA splicing.[72]

In brief, all these data highlight that miRNAs display interesting cellular activities in m6A modification through targeting m6A regulatory factors, and lay the foundation for further investigations of m6A methylation patterns in cancer pathobiology.

Impact of m6A on lncRNA regulation and function

The discovery of lncRNAs in cancer cells has provided several key insights into the underlying molecular mechanisms of malignant phenotypes.[73] Dysfunctional lncRNAs have been shown to play essential roles in cancer development and therapeutic response.[74,75]

It is well known that m6A modification is highly enriched within lncRNA sequences, and is strictly required for their

biological functions.[76] Several lncRNAs with m6A modifications display METTL3-dependent high stability and expression.[77] As expected, the m6A modification was enriched in lncRNA FAM225A and improved its transcript stability.[78] Short hairpin RNA (shRNA)-mediated silencing of METTL3 led to decreased m6A methylation of lncRNA FAM225A and further suppressed its oncogenic function in nasopharyngeal carcinoma. METTL3, along with METTL14, promoted m6A methylation of LNCAROD and improved its stability in head and neck squamous cell carcinoma (HNSCC). This subsequently stabilized LNCAROD role as a scaffold to promote YBX1-HSPA1A interaction, ultimately protecting oncoprotein YBX1 from proteasomal degradation.[79] In prostate cancer cells, overexpression of VIRMA, the regulatory component of methyltransferase complex, significantly enhanced the stability and abundance of lncRNA CCAT1/2 methylated transcripts.[80] Moreover, the unique profiles of m6A-related lncRNAs have been implicated as intriguing prognostic biomarkers for glioblastoma patients.[81] Thus, clarifying the underlying mechanisms of m6A on lncRNA modulation is essential for future diagnostic and therapeutic inventions for malignant diseases.

RNA m6A modifications can induce the structural rearrangements of lncRNAs that sequester or expose the miRNA-binding sites.[82] In HCC, m6A modification mediated by METTL3 resulted in LINC00958 upregulation via stabilization of its RNA transcript, consequently aggravating HCC lipogenesis and progression. Further biochemical analysis showed that LINC00958 contains several modification sites for m6A, which were indispensable for the recognition of miR-3619-5p.[83] Likewise, METTL3 promoted lncRNA RHPN1-AS1 expression in a m6A-dependent manner, facilitating tumorigenicity and metastasis of ovarian cancer cells.[84] Mechanistically, upregulated RHPN1-AS1 acts as a competing endogenous RNA (ceRNA) to sponge miR-596, finally increasing *LETM1* expression and activating AKT signaling pathway. Another example involves lncRNA pseudogene, Olfr29-ps1, which could affect the myeloid-derived suppressor cells (MDSC)-targeted immunotherapy.[85] It was found that m6A-modified Olfr29-ps1 enhanced its interaction with miR-214-3p and upregulated its target gene *MyD88*, thereby positively regulating the immunosuppressive function and differentiation of myeloid cells.

M6A modifications are responsible for the regulation of lncRNAs by providing the binding site for m6A "readers". IGF2BP2 served as a critical "reader" for m6A-containing lncRNA DANCR and synergistically sustained pancreatic cancer pathogenesis and resistance.[86] Meanwhile, LINC00278 was highly methylated by METTL3, which was required for YTHDF1 recognition and facilitated LINC00278 translation.[87,88] The m6A mapping study has revealed that at least 78 m6A residues were distributed in lncRNA XIST sequences.[89] METTL14-dependent m6A of XIST could be specifically recognized by YTHDF2, which led to XIST degradation and tumor inhibitory effects in CRC.[90] Conversely, methylated lncRNA PVT1 could be demethylated by ALKBH5, thereby blocking the binding of m6A "reader" YTHDF2 to PVT1.[91] In another study, YTHDF3 selectively bound to m6A-modifed lncRNA GAS5 and modulated GAS5 decay in a methylation-dependent manner. Surprisingly, GAS5 downregulation could further improve YAP-mediated transcription activation of YTHDF3.[92] These results indicate a negative feedback loop between lncRNAs and m6A "readers" in tumor progression.

M6A methylation might also be involved in lncRNA regulation by regulating its subcellular localization.[93,94] In line with this, Wu et al discovered that m6A-induced lncRNA RP11 triggered its nuclear accumulation in CRC cells. Furthermore, intranuclear lncRNA RP11 could post-translationally stimulate the expression of epithelial—mesenchymal transition (EMT)-related transcription factor Zeb1 by accelerating the mRNA degradation of two E3 ligases, Siah1 and Fbxo45.[95]

Therefore, these findings imply that the interaction between m6A epitranscriptome and lncRNA affects tumorigenesis and progression, which hence offers a potential interventional target for human cancers. Nonetheless, due to limited understanding of their functions and regulatory mechanisms, the relevance of m6A changes in lncRNAs requires additional validation, as well as functional follow-up studies.

LncRNAs regulate m6A on RNAs

Of note, RNA m6A modification can also be inversely regulated by lncRNAs, which is of great significance in modulation of cancer-associated signaling pathways and alteration of cellular fates. Particularly, several dysregulated lncRNAs exert their functions via regulation of methyltransferase complex.[9] As elucidated by Sun et al, METTL14 could be recognized and recruited by LNC942 with the specific binding domain (+176 to +265).[96] In this process, LNC942 revealed its pro-proliferation functions in breast cancer through promotion of METTL14-mediated m6A methylation and by elevating the stability of downstream targets CXCR4 and CYP1B1. In GC, lncRNA ARHGAP5-AS1 effectively recruited METTL3 to stimulate m6A modification of ARHGAP5. M6A-dependent stabilization of ARHGAP5 by ARHGAP5-AS1—METTL3 was responsible for impaired autophagy and acquired cisplatin (DDP) resistance.[97] Meanwhile, LINC00470 promoted the degradation of PTEN mRNA on the METTL3-dependent pathway to facilitate GC cell proliferation and metastasis.[98] In addition, lncRNA GATA3-AS served as a pivotal cis-regulatory element for the interaction between KIAA1429 and GATA3 nascent transcripts. With the guidance of GATA3-AS, KIAA1429 catalyzed m6A modification on the 3′-UTR of GATA3 pre-mRNA and in turn led to GATA3 downregulation in HCC cells.[99]

Both m6A "erasers" and "readers" are also decorated by lncRNAs. A number of studies has uncovered that RNA m6A demethylases rely on the lncRNA-associated regulatory mechanism to execute their functions.[100] Elevation of long non-coding RNA just proximal to the X-inactive specific transcript (JPX) could promote the aerobic glycolysis and temozolomide chemoresistance in glioma cells. Mechanistically, lncRNA JPX has been found to interact with FTO demethylase and further enhance the FTO-dependent mRNA demethylation of phosphoinositide dependent kinase-1.[101] The findings from Zhang's group demonstrated that lncRNA FOXM1-AS enhanced the interaction of ALKBH5 with *FOXM1* pre-mRNA, resulting in the demethylated *FOXM1* and oncogenic effects in glioblastoma.[102] ALKBH5

could also interact with the lncRNA SOX2OT to confer temozolomide resistance in glioblastoma cells. In the SOX2OT-overexpressed condition, ALKBH5 promoted *SOX2* expression by demethylating the *SOX2* transcripts.[103] Additionally, the oncopeptide RBRP encoded by LINC00266-1 was found to mainly bind to m6A "reader" IGF2BP1. RBRP recruited IGF2BP1 to recognize m6A-modified *c-Myc* transcripts and increased *c-Myc* oncogene expression.[104] Moreover, lncRNA CCAT2 could significantly promote the tumorigenesis of esophageal squamous cell carcinoma by downregulating miR-200b to elevate the expression of miR-200b target *IGF2BP2*.[105]

At present, these reports have emphasized the importance of lncRNAs on the m6A epitranscriptome in the aggressive phenotype of human cancers. These findings have provided the evidence for lncRNAs' influence on m6A regulators. Whether lncRNAs directly mediate their activity and expression needs further experimental verification. Even though the specific roles of lncRNA LINRIS on the regulation of IGF2BP2 protein stabilization have been preliminarily reported,[106] the underlying mechanisms are still under investigation.

Impact of m6A on circRNA signaling and function

Emerging studies have discovered circRNA as a novel endogenous ncRNAs. Unlike linear RNAs, the 3′- and 5′-terminals normally present in RNAs have been joined together, forming covalently closed continuous loop. This unique structure effectively prevents the degradation of circRNAs by ribonucleases or exonucleases, thus making them more stable.[107] CircRNAs can function as miRNA sponges or critical regulators of their parental genes. Beyond that, several circRNAs can also serve as protein-coding RNA transcripts that encode functional proteins. Although the detailed mechanisms of circRNA biology remain to be elucidated, these well-known functions have identified them as potential biomarkers and therapeutic targets in human diseases, including cancers.[108,109]

CircRNAs, especially exon-derived circRNAs, are found to be m6A-modified in human transcriptome, which is enhanced by methyltransferase complex METTL3/14 and inhibited by demethylase FTO.[110] Coincidentally, the consensus m6A recognition motif RRACH has been discovered in circRNA sequences by several independent research groups.[111,112] The genome-wide mapping and analysis of m6A circRNAs displayed that m6A modification was frequently present in circRNAs,[113] where Zhou et al identified more than one thousand m6A circRNAs in mammalian cells. The presence of m6A circRNAs was mainly dependent on the interaction between circRNAs and m6A "readers" YTHDF1/2, and could be decreased upon METTL3 depletion. Conversely, depleting m6A demethylases FTO and ALKBH5 induced a generalized increase in the abundance of m6A-containing circRNAs.[114] In addition, the m6A circRNAs were differentially expressed in diverse cell types, thus confirming the cell-type-specific patterns of circRNA methylation.[113] Meanwhile, Su et al used an m6A-seq approach to analyze the transcriptome-wide map of m6A circRNAs upon hypoxia stress, and found that hypoxia could significantly influence the m6A level of circRNAs and circRNAs abundance. Furthermore, m6A modification influenced the circRNA—miRNA-mRNA regulatory network involved in the hypoxia-driven signals in mammalian cells.[115] In CRC cells, nuclear m6A "reader" YTHDC1 bound to m6A-modified circNSUN2 and facilitated its cytoplasmic export. Consequently, the increased circNSUN2 in the cytoplasm specifically interacted with *IGF2BP2*, thus stabilizing its downstream target HMGA2 and promoting CRC cell aggressiveness.[116]

Altered m6A regulators may contribute to the aberrant expression profiles of circRNAs seen in disease pathogenesis and progression.[117,118] The majority of circRNAs are synthesized by a co-transcriptional back-splicing pattern.[119,120] Moreover, increased m6A levels correlated with correct splicing,[121] which may promote circRNA biogenesis. To prove this hypothesis, Tang et al demonstrated that the back-splicing occurred mostly at m6A sites, which were preferentially enriched near the start and stop codons in linear mRNAs.[122] Additionally, ribonuclease P/MRP, an endoribonuclease complex, has been demonstrated to facilitate the circRNAs degradation. A subset of circRNAs carrying the m6A modification could be subjected to rapid endoribonucleolytic cleavage through m6A—YTHDF2—ribonuclease P/MRP dependent mechanism.[123] A recent work conducted by Park and colleague showed that the endoribonucleolytic cleavage mediated by YTHDF2—HRSP12—ribonuclease P/MRP axis was applicable to m6A-containing circRNA decay. Knockdown of adaptor protein HRSP12 or ribonuclease P/MRP significantly abrogated the degradation of YTHDF2-bound circRNAs.[124] YTHDF2 also recognized m6A-containing ncRNAs, and accelerated their destabilization via CCR4—NOT complex-mediated deadenylation pathway.[125] Despite the important implications, the comprehensive molecular mechanisms of m6A RNA methylation responsible for the circRNA biogenesis and decay remain poorly understood, and thus warrant further research.

Several latest reports revealed that methylated circRNAs display protein-encoding potential in a cap-independent pattern, and their translated products can offer a novel perspective for a variety of pathophysiological contexts.[126,127] Interestingly, a single m6A site sufficiently initiated circRNA translation in eukaryotic cells by directly recruiting the eukaryotic translation initiation factors (eIFs) and m6A regulators.[128] Especially, the direct binding of 5′UTR m6A to eIF3 subsequently promoted translation in the absence of cap-binding factor eIF4E.[129] Upon specific environmental stress, the m6A in 5′UTR of RNA transcripts was reported to regulate the ribosomal scanning and start codon selection, thereby driving the non-classical cap-independent translation mechanism.[130] This concept has been strongly enhanced using m6A-seq method, and demonstrates that circRNAs can be efficiently translated using short sequences carrying the consensus m6A residues in human cells.[131,132] For example, circ-ZNF609 was previously demonstrated to contain an open reading frame and can undergo translation.[133] The translation ability of circ-ZNF609 could be effectively controlled through recognition by m6A "reader" YTHDF3 and eIF4G2.[134] The circE7 generated from oncogenic human papillomaviruses (HPVs) was preferentially m6A-modified and translated to produce E7 oncoprotein, which then accelerated the phenotype

transformation of cervical carcinoma CaSki cells.[135] Therefore, all these findings suggest that m6A-mediated translation initiation can serve as a potential driving mechanism for circRNA translation, enlightening the need to characterize the complexity of translated circRNAs in the pathological changes of cancer cells.

Although m6A epitranscriptional modification has been confirmed for its enrichment and biological importance in modulating circRNAs in cancer pathogenesis,[136] the underlying regulatory networks of m6A-circRNAs have not been fully elucidated so far. More detailed evaluations are needed to clarify the putative relationships between m6A-epitranscriptomes and circRNA-dependent signaling events. Particularly, it is of interest to note that m6A methylated circRNAs have permanently extended our attention towards cancer pathological behaviors, especially in tumorigenesis and treatment.

CircRNAs regulate m6A on RNAs

Interestingly, abnormal level of circRNAs might also regulate m6A abundance in cancer cells and further influence cancer phenotypes. CircRNAs can function as efficient miRNA sponges by competitively binding to miRNA response elements (MREs) to suppress their activity, resulting in increased levels of miRNA targets.[137,138] Given the potential regulatory roles of miRNAs on m6A modification,[139] we hypothesize that to some extent, circRNAs might modulate m6A modification in miRNA-dependent manner. A recent study established the circRNA—miRNA—METTL14 interaction network in kidney renal clear cell carcinoma (KIRC) supporting this hypothesis. The findings from this research showed that circRNAs regulated m6A methyltransferase METTL14 by sponging multiple miRNAs involved in the occurrence and progression of KIRC.[140] However, another study reported the direct interaction between circRNAs and m6A regulators. In dysfunction astrocytes, overexpression of circSTAG1 abolished the translocation of *ALKBH5* into the nucleus by capturing ALKBH5, and further promoted the m6A-mediated degradation of *FAAH* transcripts.[141] These studies preliminarily provided proof-of-concept evidence for the functional roles of circRNAs on m6A modulation, and shed novel insights into the development of preventive strategy for cancers. Nevertheless, the potential regulatory mechanisms need further clarification with research on the functional link between circRNAs and m6A epitranscriptional modification.

Interplay of m6A-ncRNA related to immune system

The cells in innate and adaptive immune system have been reported to exert regulatory effects on the development and progression of cancer. In addition, m6A modification has been implied as a vital regulator of the immune system and to be involved in various aspects of immune-related disorders, including cancer.[142,143] M6A methylation of N6-adenosine frequently occurs in immunological disorders-associated ncRNAs, including miRNAs, and consequently changing their mechanisms of action in the immune response[144] (Table 1). As an important regulator for m6A modification, miR-142 overexpression had been proven to improve the HCC patients' prognosis through interference in the abundance of tumor-infiltrating immune cells.[145] Thus, the relationship between m6A-modifiers and ncRNAs can potentially be used to reprogram the tumor microenvironment (TME) by modulating the immune-associated signatures, hence, interfering with the cancer immunotherapeutic procedures.[146,147]

Several recent reports discussed the promising roles of lncRNA—m6A interaction networks in host immune response, and suggested probable clinical applications.[148,149] Upregulated C—C motif chemokine receptor 7 (CCR7) inhibited the degradation of lnc-Dpf3 by promoting its demethylation, resulting in suppression of dendritic cell migration and prevention of aberrant inflammatory responses.[150] Li et al evaluated the m6A modification pattern of lncRNAs in pro-inflammatory (M1-L) and anti-

Table 1 M6A-ncRNA interaction in the regulation of cancer immune response.

M6A-ncRNAs	Immune regulation	Biological behaviors	Refs
MiR-142	Affecting immune cell infiltration	Functioning as m6A regulator	145
11 m6A-related lncRNAs	Modulating immune checkpoint inhibitors	Involving in immunotherapy	149
Demethylated Lnc-Dpf3	Suppression of dendritic cell migration	Prevention of aberrant inflammatory responses	150
244 m6A-modified lncRNAs	Regulating cellular immune system	Regulators for pro-inflammatory and anti-inflammatory response	151
M6A-related lncRNA signature	Affecting immune cell infiltration	A promising immune prognostic model	142
M6A modified circRNAs	Blunting the immunogenicity of circRNAs	Inhibiting innate immunity	156
CircZbtb20	Promoting m6A-demethylation of Nr4a1 mRNA that is required for function of innate lymphoid cells	Maintaining innate lymphoid cell homeostasis	157
M6A-modified circNDUFB2	Recruiting immune cells into tumor microenvironment	Facilitating anti-tumor immunity	158

inflammatory (M2-L) cells. 244 lncRNAs were differentially methylated with m6A between M1-L and M2-L cells. Moreover, these differentially m6A-modified lncRNAs mainly participated in the regulation of cellular immune system and signal transduction.[151] Through comprehensive analyses of the profiles of m6A-related lncRNAs in the immune regulation of HCC, Yu et al identified a m6A-related lncRNA signature as a promising immune prognostic model.[152] Moreover, higher levels of several immune cells, such as activated memory $CD4^+$ T cells, $CD8^+$ T cells and follicular T-helper cells, were shown to infiltrate the TME of high-risk patients, revealing that higher density of tumor-infiltrating immune cells may affect the response to immunotherapy. Therefore, clarifying the biological roles of m6A—lncRNA interactions in immune regulation might elucidate important scientific knowledge in the understanding of novel therapeutic and prognostic targets for cancer patients.

It was presented that the frequently expressed circRNAs in eukaryotic cells makes them potential therapeutic biomarkers for the antitumor immunity.[153] M6A modification has been revealed to significantly blunt the immunogenicity of circRNAs in human cells, and serves as potent contributor in regulating circRNA-associated immune signaling.[154] In line with the observations, recent studies have demonstrated that antitumor immunity can be effectively controlled by m6A methylation-dependent processes. Loss of YTHDF1 in dendritic cells increased the production of interferon-γ (IFN-γ), followed by the activation of cytotoxic T cells and tumor inhibition.[155] Meanwhile, YTHDF2 interacted with m6A sites in circRNAs to suppress the antigen-specific T cell activation and antitumor immunity *in vivo*.[156] Liu et al demonstrated the essential roles of circZbtb20 for maintenance of innate lymphoid cell homeostasis. Mechanistically, circZbtb20 enhanced ALKBH5-mediated demethylation of *Nr4a1* mRNA, improving *Nr4a1* stability and its downstream Notch2 signaling, which were required for the functions of innate lymphoid cells.[157] During the progression of non-small-cell lung cancer (NSCLC), m6A-modified circNDUFB2 facilitated the anti-tumor immunity by eliciting the polyubiquitination-mediated degradation of IGF2BPs.[158] Collectively, these data show that interfering with m6A-modified circRNAs may be efficient in improving the immunotherapy outcomes in cancer patients.

M6A-ncRNA interaction in the regulation of cancer therapeutic resistance

Therapeutic resistance has been identified as a major obstacle to the treatment of patients with malignancies. Cancer therapeutic resistance is a complex phenomenon that can be influenced by multiple mechanisms, such as tumor heterogeneity, epigenetic modification, genetic alteration, etc. Emerging studies have revealed that m6A—ncRNAs interaction serves as an important biological process involved in the treatment of multiple human diseases, including cancers.[159,160] In recent years, the functions of m6A—ncRNA interaction in cancer therapeutic resistance regulation have been evaluated, and the specific molecular mechanisms have been partially discovered.[161] Regulation of m6A—ncRNA-dependent signaling events can successfully limit cell growth and overcome therapeutic resistance of cancer cells,[162,163] suggesting that understanding of m6A—ncRNAs association might be useful for proposing promising strategies for cancer treatment (Table 2). However, because of the unexplored mechanisms underlying the interaction between m6A and ncRNAs, the application of RNA modification regulatory factors in cancer therapy is limited in clinical practice.

The RNA "writer" METTL3 has been proven to regulate miRNA metabolism, contributing to therapeutic resistance in cancer cells. In MCF-7 breast cancer cells, METTL3 overexpression stimulated pre-miR-221-3p maturation in a m6A-dependent manner, reduced cell apoptosis and sustained doxorubicin resistance.[164] Surprisingly, miR-4443 bound METTL3 and downregulated its activities, suggesting that METTL3 was a direct target of miR-4443. High level of exosome-derived miR-4443 conferred DDP resistance in NSCLC cell line A549-R via interference of METTL3-mediated m6A methylation of FSP1.[165] Accumulating evidence confirmed the important roles of lncRNAs in cancer therapeutic resistance through sponging of miRNAs and regulating their downstream targets. METTL3-mediated m6A modification of lncRNA MALAT1 markedly enhanced its stability, functioned as miR-1914-3p sponge and subsequently enhanced the expression of downstream target *YAP*, thereby promoting lung cancer metastasis and DDP resistance.[63] In addition, forkhead box O3 (FOXO3)-induced lncRNA LOC554202 bound to miR-485-5p and impaired its tumor-promoting function in HCC.[166] Since *FOXO3* is a downstream target of METTL3, Lin et al found that METTL3 knockdown enhanced sorafenib resistance of HCC by abolishing the *FOXO3* methylation and its downstream signaling.[167] Moreover, using lncRNA microarray, Gu and colleague analyzed lncRNA expression profiles and identified the highly-expressed LINC00922 in doxorubicin-resistant osteosarcoma cells MG63/DXR.[168] Mechanistic assays indicated that METTL3-mediated m6A methylation enhanced the stability of *transcription factor activating protein 2 gamma (TFAP2C)* in resistant sarcoma cells.[169] Concurrently, overexpressed *TFAP2C* promoted the transcription of LINC00922, contributing to chemotherapy resistance.[168] In GC, lncRNA ARHGAP5-AS1 recruited METTL3 to accelerate m6A modification of *ARHGAP5* mRNA and promote its stabilization in the cytoplasm. Blocking lncRNA ARHGAP5-AS1/ARHGAP5 signaling axis significantly decreased DDP resistance and improved therapeutic outcome, which might provide a promising strategy to overcome chemoresistance.[97] In addition, m6A-mediated circCUX1 stabilization relies on the m6A reader METTL3. Knockdown of METTL3 by siRNA significantly reversed the expression of oncogenic circCUX1, thereby promoting cell apoptosis and reversing radiotherapy resistance in hypopharyngeal squamous cell carcinoma (HPSCC).[170] Similarly, METTL3 depletion resulted in decreased m6A methylation of circRNA-SORE, thereby deactivating the Wnt/β-catenin pathway and increasing sorafenib sensitivity in HCC.[171] However, the detailed regulation and function of circRNAs on METTL3 in treatment resistance are largely unknown and remain to be explored.

Serving as a representative RNA "eraser", the demethylase ALKBH5 can lead to the demethylation of cancer-associated ncRNAs, affecting the tumorigenicity and treatment efficacy.[172] Exosomal circ_0072083 competitively sponges miR-1252-5p to enhance its *ALKBH5* targeting in

Table 2 The interaction between m6A and ncRNA in cancer therapeutic resistance.

M6A regulators	NcRNAs	Functions	Therapeutic responses	Cancers	Refs
METTL3	MiR-221-3p	Stimulating pri-miR-221-3p maturation	Sustaining doxorubicin resistance	Breast cancer	164
METTL3	MiR-4443	Interfering METTL3-mediated FSP1 m6A methylation	Conferring cisplatin resistance	Lung cancer	165
METTL3	LncRNA MALAT1	Enhancing MALAT1 stability	Conferring cisplatin resistance	Lung cancer	63
METTL3	LOC554202	Promoting FOXO3 methylation and its downstream LOC554202	Inhibiting sorafenib resistance	Hepatocellular carcinoma	166
METTL3	LINC00922	Enhancing TFAP2C stability and promoting LINC00922 transcription	Promoting doxorubicin resistance	Osteosarcoma	168,169
METTL3	LncRNA ARHGAP5-AS1	Increasing M3TTL3-mediated ARHGAP5 stabilization	Conferring cisplatin resistance	Gastric cancer	97
METTL3	CircCUX1	Enhancing circCUX1 stability	Reversing radiotherapy resistance	Hypopharyngeal squamous cell carcinoma	170
METTL3	CircRNA-SORE	Increasing m6A level of circRNA-SORE	Promoting sorafenib resistance	Hepatocellular carcinoma	171
ALKBH5	Circ_0072083	Increasing ALKBH5 expression	Promoting temozolomide resistance	Glioma	173
FTO	LncRNA HLA-F-AS1	Activation STAT3 and inducing HLA-F-AS1 expression	Facilitating doxorubicin resistance	Breast cancer	174,175
HNRNPA2/B1		Results in a significant change in multiple miRNAs	Promoting tamoxifen resistance	Breast cancer	60

temozolomide-resistant glioma cells U251/TR and U87/TR. The circ_0072083 silence evidently decreased the *ALKBH5* expression and reduced ALKBH5-mediated demethylation of nanog homeobox (NANOG), facilitating apoptosis and suppressing growth of temozolomide-resistant cells *in vivo* and *in vitro*.[173] The m6A "eraser" FTO facilitated doxorubicin resistance of breast cancer cells by controlling the activation of signal transducer and activator of transcription 3 (STAT3) signaling.[174] Moreover, STAT3-induced lncRNA HLA-F-AS1 enhanced cell viability and induced poor therapeutic effect.[175] In addition, the m6A "reader" HNRNPA2/B1 was shown to be remarkably upregulated in tamoxifen-resistant breast cancer LCC9 cells. Whole genome miRNA profiling revealed that overexpression of HNRNPA2/B1 resulted in a significant change in multiple miRNAs, affecting several signal pathways associated with endocrine therapy resistance, such as transforming growth factor β (TGFβ) signaling.[60] Taken together, these findings support the fundamental roles of m6A—ncRNAs interaction in the processes that contribute to therapy resistance in human cancers.

Databases for m6A-ncRNA analysis in cancer research

Nowadays, identifying the accurate features of the m6A methylome among mammalian systems is still a major challenge. Especially, there are significant requirements for new computational tools to analyze the data from methylated RNA immunoprecipitation combined with RNA sequencing (MeRIP-seq) to gain further insight into the functional links between RNA methylation and ncRNAs.[13] In recent years, some available algorithms have been developed to annotate and identify the interaction networks between m6A modifications and ncRNAs (Table 3). These user-friendly databases enable more convenient acquisition of m6A—ncRNA interaction by using different computational methods, which can be used in additional research. The MethylTranscriptome DataBase (MeT-DB) is the first comprehensive resource for interrogating m6A methyltranscriptome from all published MeRIP-seq datasets. More importantly, this database also offers a genome browser to query and visualize the context-specific m6A with miRNAs and their target genes.[176,177] The website RMBase offers a variety of interfaces and graphic visualizations to facilitate analyses of the relationships between m6A modification and multiple types of genes, including miRNAs and lncRNAs. This web-tool can also be an applicable strategy for mapping RNA modifications in normal tissues and cancer cells.[178,179] Recently, M6A2Target was constructed to identify potential lncRNA targets and regulators of m6A RNA methylation.[180] Furthermore, the hierarchical model MeTCluster, developed by Cui et al, can systematically uncover and cluster the m6A methylation peaks in lncRNAs with high accuracy and good sensitivity.[181] Similarly, MeTDiff is another novel computational tool for predicting the differential m6A methylation

Table 3 The databases and analysis tools for m6A-ncRNA interaction in cancer research and treatment.

Databases	Characteristics	URL	Refs
MeT-DB	Interrogating the context-specific m6A with the binding sites of miRNAs	http://compgenomics.utsa.edu/MeTDB/	177
RMBase	Analyzing the relationships between m6A modification and miRNAs/lncRNAs	http://rna.sysu.edu.cn/rmbase/	179
M6A2Target	Confirming lncRNAs as potential targets of m6A regulators	http://m6a2target.canceromics.org	180
MeTCluster	Clustering the specific m6A methylation peaks in lncRNAs	http://compgenomics.utsa.edu/metcluster	181
MeTDiff	Predicting the m6A methylation sites on human lncRNAs	https://github.com/compgenomics/MeTDiff	182
LncVar	Systematically integrating the statistics of SNPs in m6A regions on lncRNAs	http://bioinfo.ibp.ac.cn/LncVar	183
CVm6A	Exploring the cell-dependent m6A patterns in lncRNAs	http://gb.whu.edu.cn:8080/CVm6A	184
LITHOPHONE	Scanning the entire human lncRNAome for all possible lncRNA m6A sites	http://180.208.58.19/lith/	185
Circbank	Visualizing the difference of m6A modification between circRNAs and its host gene	http://www.circbank.cn/	186

sites on human lncRNAs with higher sensitivity and specificity.[182] Utilizing these two algorithms, researchers confirmed that the methylation density with less peak enrichment are more likely to be distributed at the 5′-end of lncRNAs, while those with higher peak enrichment tend to cluster at the 3′-end of lncRNAs. These results indicate that m6A's functions in lncRNA regulation could be location specific. In addition, a newly constructed tool, LncVar, can be used to systematically integrate the effects of single nucleotide polymorphisms (SNPs) in m6A regions on lncRNAs from six species (*Homo sapiens*, *Mus musculus*, *Danio rerio*, *Caenorhabditis elegans*, *Drosophila melanogaster* and *Arabidopsis thaliana*).[183] CVm6A software proposes a quantitative detection method to visualize the cell-dependent m6A patterns in mRNAs and lncRNAs. In particular, CVm6A can also be used to distinguish the unique m6A profiles in cancer and non-cancer cells.[184] The study by Liu and colleague presents another computational framework, LITHOPHONE, for scanning the entire human lncRNAome for all possible lncRNA m6A sites. Using the Ensemble predictor algorithm, they can achieve the best performance for identifying lncRNA methylation sites in a non-biased way.[185] Circbank, designed by Liu's group, is a comprehensive database for circRNA with the standard nomenclature, which can alleviate the terminological confusion for both bioinformatic and experimental circRNA research. Of note, Circbank can also visualize the difference of m6A modification between circRNAs and their host genes.[186] Although other m6A-associated algorithms, such as m6AVar,[187] REPIC,[188] SRAMP[189] and WHISTLE,[190] have not been utilized to detect the m6A peaks in ncRNAs currently, these databases would provide more strategies for comparison, eventually leading to a more accurate landscape of the m6A methylation in transcriptome. Moreover, some challenges exist across these algorithms, where there is no clear-cut golden standard and non-overlapping predicted behaviors,[107] should be addressed with further high-quality studies. Consequently, addressing these challenges is important for using bioinformatics approaches to appropriately validate the prediction findings.

Conclusion and future remarks

RNA m6A modification draws much attention, and has diverse regulatory roles on ncRNAs, such as their biogenesis, degradation, expression, etc. Growing evidence shows that the m6A—ncRNA regulatory networks are prevalent features of cancer cells and likely to have important biological functions in disease development and treatment. More detailed studies on the association between m6A status and ncRNAs would provide the novel insights on how their interactions affect tumorigenesis, immune regulations and therapeutic responses. Considering that various molecular pathways during cancer pathogenesis can be triggered following m6A—ncRNA signaling, a better understanding of the underlying regulatory mechanisms in different cell-types and stimuli remains to be achieved. Meanwhile, the clarification of m6A—ncRNA regulatory networks may also have clinical implications and prognostic significance, which is an under-studied field demanding further investigations. More importantly, it will be worthwhile determining how cancer cells can accurately respond to different therapeutic strategies mediated by the m6A—ncRNA signaling pathways. Eventually, comprehensive and detailed knowledge of these issues will open new therapeutic avenues to effectively intervene in the m6A—ncRNA signaling for cancer cell elimination.

Author contributions

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Conflict of interests

The authors declare no conflict of interests.

Funding

This work was supported by The National Natural Science Foundation of China (No. 81803035); The China Postdoctoral Science Foundation (No. 2021T140754 and 2020M672521); The Natural Science Foundation of Hunan Province, China (No. 2020JJ5934); and The Postdoctoral Science Foundation of Central South University, China (No. 248485).

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