Crosstalk between RNA m6A Modification and Non-coding RNA Contributes to Cancer Growth and Progression

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N6-methyladenosine (m6A) is the most common RNA modification and has an important role in normal development and tumorigenesis. The abnormal expression of m6A regulators can lead to an imbalance in m6A levels in cancer cells, leading to the dysregulated expression of oncogenes and tumor suppressor genes that may contribute to cancer development, patient response to chemoradiotherapy, and clinical prognosis. Recent studies demonstrate that non-coding RNAs are involved in epigenetic modification of both DNA and RNA in tumor cells, and may also affect the development and progression of cancer by targeting m6A regulators. In this review, we describe the functional crosstalk between m6A and non-coding RNAs, particularly microRNA, long non-coding RNA, and circular RNA, and illustrate their roles in tumor regulation. Finally, we discuss the significance of non-coding RNA and m6A modification in the diagnosis, treatment, and prognosis of cancer patients, as well as potential future research directions.

According to recent global cancer statistics, cancer remains an important factor threatening human health.1 N6-methyladenosine (m6A) is the most common RNA modification and has attracted significant attention from researchers in the fields of tumorigenesis and development.2-7 Since the discovery of m6A in the early 1970s, studies have shown that it accumulates predominantly near the stop codons and 3' untranslated regions (3' UTRs) of mRNA.8-10 The abnormal expression of m6A regulators can lead to an imbalance in m6A levels in cancer cells, leading to the dysregulated expression of oncogenes and tumor suppressor genes that may contribute to cancer development, patient response to chemoradiotherapy, and clinical prognosis.2,7,9,10

Previous studies confirm that dysregulation of m6A regulators may be detected in precancerous lesions, highlighting their potential as molecular markers for the early diagnosis of cancer.11 Fat mass and obesity-associated protein (FTO) has been identified as an m6A demethylase that can selectively remove the m6A modification from target RNAs.12 A recent study showed that combination of FTO inhibitor and nilotinib can restrain the growth of leukemia and increase the sensitivity of leukemia cells to tyrosine kinase inhibitors, highlighting the potential therapeutic value of targeting m6A regulators in drug-resistant cancers.13 Although the FTO inhibitor, entacapone, has been approved by The Food and Drug Administration (FDA) for the treatment of cancer and other related diseases,13 specific inhibitors have not yet been identified for other m6A regulatory proteins.

Although the function of m6A modification in cancer is becoming increasingly clear, its effect on protein translation and the molecular mechanisms underlying the effect of this mark on cancer progression remain unclear. Following the development of MeRIP-seq (methylated RNA immunoprecipitation sequencing) and miCLIP (m6A individual-nucleotide-resolution cross-linking and immunoprecipitation) technologies, researchers have found that non-coding RNAs, including

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long non-coding RNA (lncRNA), microRNA (miRNA), circular RNA (circRNA), transfer RNA, ribosomal RNA, and small nuclear RNA, are also capable of modifying DNA and RNA bases in cancer cells.\textsuperscript{15,16} Furthermore, non-coding RNA also participates in the regulation of m\textsubscript{6}A modification, thus affecting cancer progression (Figure 1).\textsuperscript{3,17}

In this review, we describe the functional crosstalk between m\textsubscript{6}A and non-coding RNA, particularly miRNA, lncRNA, and circRNA, and illustrate how deregulation of these networks plays a role in tumors. Finally, we discuss the significance of non-coding RNA and m\textsubscript{6}A modifications in the diagnosis, treatment, and prognosis of cancer patients and possible future research directions.

**Overview of m\textsubscript{6}A Writers, Erasers, and Readers**

m\textsubscript{6}A modification is a dynamic and reversible process that has a critical role in regulating RNA stability, splicing, and translation. This modification is controlled by regulatory proteins referred to as “writers,” “erasers,” and “readers” (Figure 2). Epigenetic writers included methyltransferase-like 3/14/16 (METTL3/14/16), wt1-associated protein (WTAP), RNA binding motif protein 15/15B (RBM15/15B), and vir-like m\textsubscript{6}A methyltransferase-associated protein (VIRMA, also known as KIAA1429). METTL3/14 can form complexes to cause m\textsubscript{6}A methylation to be written into mRNA,\textsuperscript{18} and WTAP aids METTL3/14 to locate nuclear spots and maintain the catalytic activity of m\textsubscript{6}A methyltransferase \textit{in vivo}.\textsuperscript{19} Meanwhile, METTL3 expression is essential for WTAP protein homeostasis.\textsuperscript{20} Moreover, RBM15, RBM15B, and VIRMA have roles in the regulation of METTL3 and METTL14 activity.\textsuperscript{21}

Erasers include FTO and AlkB homolog 5 (ALKBH5). These proteins can selectively remove the m\textsubscript{6}A mark targeting mRNA through a series of complex intermediate reactions, thereby affecting tumor-specific biological processes.\textsuperscript{22} In 2001, researchers from the laboratory of Chuan He confirmed that FTO is an important DNA and RNA demethylase, particularly for m\textsubscript{6}A demethylation.\textsuperscript{12} The oncogenic role of FTO has since been confirmed in numerous cancers, including cervical cancer, breast cancer (BRC), and gastric cancer (GC).\textsuperscript{23–25}

To date, several hypotheses have inferred that m\textsubscript{6}A modifications function by altering RNA structure or recruiting m\textsubscript{6}A readers. The most common readers include m\textsubscript{6}A RNA binding protein 1/2/3 (YTHDF1/2/3), YTH domain-containing 1/2 (YTHDC1/2), insulin-
like growth factor 2 mRNA binding proteins 1/2/3 (IGF2BP1/2/3), heterogeneous nuclear ribonucleoproteins (HNRNPs), and zinc-finger CCCH domain-containing protein 13 (ZC3H13). Reader proteins function by binding to m6A sites on the target RNA and mediating its modification, thereby controlling RNA fate.

Recently, studies have highlighted the impact of m6A RNA methylation regulators on the diagnosis and prognosis of cancer patients (Table 1). Du et al. performed univariate Cox regression analysis to evaluate the clinical prognostic values of m6A RNA methylation regulators in glioblastoma (GBM), and revealed that HNRNPC, ALKBH5, and ZC3H13 are favorable prognostic markers, whereas FTO is an unfavorable prognostic marker for GBM. Furthermore, METTL3, YTHDC2, and YTHDF2 were identified as independent predictors of overall survival in liver cancer (LC). Zhuang et al. built a 10-gene risk score model in lung adenocarcinoma (LUAD) through combined analysis of expression levels of m6A RNA regulators and clinicopathological characters. They found that the expression patterns of ALKBH5, FTO, HNRNPC, YTHDF2, YTHDF1, YTHDC2, RBM15, KIAA1429, WTAP, and METTL3 were correlated with TNM stage, lymph node stage, and sex, as well as the living status of patients with LUAD. A two-gene signature consisting of METTL3 and METTL14 was identified as an independent prognostic indicator for distinguishing clear cell renal cell carcinoma (ccRCC) patients. These studies suggested that m6A regulators are potential diagnostic and prognostic markers for various cancers.

m6A Modification of Non-coding RNA

Non-coding RNAs comprise a large class of RNA transcripts without protein-coding potential that regulate gene expression and are important regulators of cancer cell proliferation, apoptosis, migration, immune response, and autophagy. m6A modification of non-coding RNA regulates important processes controlling RNA function, including processing, stability, and transport (Figure 3).

m6A Modification of miRNA

On the basis of our current understanding, miRNA biogenesis can be divided into three steps. In the nucleus, RNA polymerase II or III transcribes miRNA-related genes into primary miRNA (pri-miRNA).
Since then, numerous studies have indicated that abnormal methylation and inhibition of translation. In 2002, the Croce team identified the importance of the m6A writer METTL3 on cancer cell activity (Table 3). In HCC, METTL3-mediated m6A leads to upregulation of LINC00958 by enhancing its stability, thereby promoting cancer progression. METTL3 has also been shown to affect miRNA levels. In conclusion, m6A modification plays an important role in miRNA biogenesis, and the effects of m6A-mediated miRNA level variation require further investigation.

### m6A Modification of IncRNA

The role of IncRNA in tumor development is complex and diverse. IncRNAs may regulate gene transcription via binding to gene promoters, affect the variable splicing of RNA and maintain the normal function of intracellular organelles, act as mRNA sponges, relieving inhibition of miRNA target genes, and affect the stability and translation of mRNA via RNA interactions. They can also affect protein function by acting as a scaffold for protein-protein interactions, modulating their localization to chromatin, and regulating protein post-translational modifications and stability. IncRNAs are located in different subcellular structures, including the cell membrane, cytoplasm, nucleus, and paraspeckles, and their functions and regulatory mechanisms are closely related to their localization in cancer cells.

The synthesis and function of miRNAs may be affected by m6A modification at multiple levels (Table 2). Studies by Alarcón et al. indicate that heterogeneous nuclear ribonucleoproteins A2/B1 (HNRNPA2B1) can read m6A marks and enhance DGC8 binding to pri-miRNA transcripts, affecting miRNA processing. Similarly, the m6A writer METTL14 can interact with DGC8 and promote mIIR-126 processing in an m6A-dependent manner in hepatocellular carcinoma (HCC). In bladder cancer, METTL3 is overexpressed and regulates the processing of miR-221/miR-222 in an m6A-dependent manner via recruitment of DGC8. METTL3 also promotes pri-miR-1246 maturation via a similar mechanism and positively modulates tumor cell metastasis. Studies by Zhang et al. emphasize the importance of the m6A writer METTL3 on miR-25-3p maturation and identified NKAP as an m6A reader for pri-miR-25 processing in pancreatic cancer (PAC). METTL3 can accelerate the brain metastasis of cancer cells and promote the splicing of pre-miR-143-3p to produce mature miRNA, and may be associated with Dicer in lung cancer (LCA). As previously discussed, m6A promotes miRNA maturation by regulating its processing, thereby enhancing the degradation and translational inhibition of downstream target miRNAs. Interestingly, m6A modifications can also protect mRNA degradation mediated by miRNA. Müller et al. demonstrated that IGF2BP1 affects miRNA-directed decay of SRF mRNA, increasing SRF expression in an m6A-dependent manner. In colorectal cancer (CRC), IGF2BP2 maintains RAFI mRNA stability by blocking miRNA-mediated degradation, thereby increasing cancer cell proliferation. Furthermore, m6A modification of AGO2 mRNA has also been reported to affect miRNA levels. In conclusion, m6A modification plays an important role in miRNA biogenesis, and the effects of m6A-mediated miRNA level variation require further investigation.

### Table 1. Impact of m6A Modification Regulator on Diagnosis and Prognosis of Cancer Patients

| Cancer Type | m6A Regulator | Diagnosis/Prognosis | References |
|-------------|---------------|---------------------|------------|
| GBM         | HNRNPC, ZC3H13, ALKBH5 | unfavorable prognostic marker | 10         |
|             | FTO           | favorable prognostic marker |            |
| LC          | METTL3, YTHDC2, YTHDF2 | unfavorable prognostic marker | 28         |
| LUAD        | ALKBH5, HNRNPC, YTHDF2, YTHDF1, YTHDC2, RBM15, KIAA1429, WTAP, METTL3, FTO | diagnostic marker, prognostic marker | 29         |
| ccRCC       | METTL3        | unfavorable prognostic marker | 30         |
|             | METTL14       | favorable prognostic marker |            |

The m6A modification of IncRNA regulates numerous processes affecting cancer cell activity (Table 3). In HCC, METTL3-mediated m6A leads to upregulation of LINC00958 by enhancing its stability, thereby promoting cancer progression. METTL3 has also been shown to increase the stability of FAM225A, a IncRNA overexpressed in nasopharyngeal carcinoma (NPC), to promote tumorigenesis. Moreover, studies have shown that METTL3 can upregulate expression of RP11 IncRNA by increasing its nuclear accumulation in CRC. The m6A eraser ALKBH5 has been shown to act as both a tumor suppressor and promoter, and has the ability to demethylate m6A on single-stranded RNA and DNA. As a tumor suppressor, ALKBH5 is significantly downregulated in PAC, and its expression is related to patient survival, as well as being an independent marker of prognosis. ALKBH5 can also regulate the expression of KCNK15-AS1 via demethylation, leading to inhibition of PAC cell migration and invasion. ALKBH5 also plays a role in tumor progression, promoting osteosarcoma (OST) cell proliferation via upregulation of IncRNA PVT1. Additionally, ALKBH5 is upregulated in GC cells and increases invasion and metastasis via inhibition of NEAT1 methylation. The m6A readers IGF2BP2 and YTHDF3 are also involved in the regulation of IncRNA. IGF2BP2 is highly expressed in PAC and interacts with IncRNA DANCER, leading to an increase in its stability and promoting cancer cell proliferation. In a similar manner, YTHDF3 can negatively regulate GAS5 IncRNA and promote progression of CRC.

In the nucleus, IncRNAs may recruit regulatory proteins and interact with miRNAs or act as competing endogenous RNAs (ceRNAs), regulating the translation and stability of miRNA. Therefore, we infer that m6A modifications may affect similar regulatory functions of IncRNAs.
Figure 3. m^6A Modifications in Non-coding RNA
(A) m^6A modification regulates miRNA processing. (B) m^6A modification regulates IncRNA stability and nuclear accumulation. (C) m^6A modification regulates circNSUN2 transport.
cytoplasmic lncRNAs. However, our understanding of m6A modifications of IncRNA is still limited.

**m6A Modification of circRNA**

circRNA was first identified in eukaryotes nearly 40 years ago and was subsequently discovered in humans infected with hepatitis delta virus (HDV). Studies demonstrated that circRNA can specifically adsorb and bind miRNA, releasing the inhibition of miRNA on downstream target genes and directly binding proteins to modulate their function. In human cancer, circRNA regulates critical cellular processes, including proliferation, metastasis, differentiation, autophagy, and drug resistance.

Recent studies revealed that circRNA has the potential to be translated. Yang et al. demonstrated that m6A levels in circRNA can promote efficient initiation of protein translation from human cells. Other studies have shown that YTHDF1 and YTHDF2 can interact with circRNAs, and that METTL3 also affects circRNA m6A levels, suggesting that m6A is modified by the same machinery in both circRNAs and mRNAs. However, enrichment of m6A in circRNAs is mainly at the translation start site of their corresponding mRNAs, differing from mRNA. The m6A reader YTHDC1 has been shown to increase circNSUN2 export to the cytoplasm (Table 4), leading to the formation of a circNSUN2-IGF2BP2-HMGA2 RNA-protein ternary complex that can stabilize HMGA2 mRNA and enhance colorectal liver metastasis. Another study also reports that METTL3 can impact circZNF609 m6A modification, and YTHDC1 regulates backsplicing of circZNF609, which highlights the critical role of m6A modification in circZNF609 biogenesis and translation in HeLa cells. These studies provide a new perspective on m6A modification of circRNA.

**Regulation of m6A Modification by Non-coding RNAs**

miRNA Affects m6A Modification

Studies have shown that m6A modifications can be controlled by miRNA levels (Table 5). In LCA, miR-600 decreases the expression of METTL3 and reverses the effect of METTL3 on cancer cell progression. In keeping with these findings, miR-33a targeting of the METTL3 3’ UTR leads to the downregulation of METTL3 expression and suppression of non-small cell lung cancer (NSCLC) proliferation. Let-7g miRNA can also inhibit METTL3 expression by targeting its 3’ UTR; moreover, HBXIP increases METTL3 expression by restraining let-7g in CRC. Yang et al. reveal that overexpression of miR-145 strongly increases m6A levels via targeting of the 3’ UTR of YTHDF2 in HCC (Figure 4A). Together, these studies indicate that miRNAs may affect m6A modification by controlling the levels of m6A regulators.

**IncrRNAs Regulate m6A Modification**

As discussed above, m6A modification participates in IncRNA biogenesis and can affect functional activity. Conversely, IncRNAs can also affect m6A regulators and influence their function in cancer cells (Table 6). For example, the IncRNA LINRIS is upregulated in CRC cells and maintains IGF2BP2 protein stability via blocking the ubiquitination–proteasome pathway. ALKBH5 is highly expressed in primary GBM cell lines and promotes cancer cell proliferation. The IncRNA FOXM1-AS promotes the interaction between ALKBH5 and FOXM1, leading to demethylation of FOXM1 mRNA and overexpression of FOXM1 (Figure 4B). These studies suggest that regulation of m6A modifications by antisense IncRNAs may be a common mechanism. As a regulatory subunit of IGF2BP1, the peptide RBRP encoded by LINC0266-1 can recognize m6A modification via binding
to IGF2BP1 and recruit stable RNA molecules to maintain the stability of MYC mRNA, thus promoting the occurrence and development of tumors.\(^8^5\) This study enriches our understanding of the effect of IncRNA on m\(^6\)A modification.

### Conclusions

m\(^6\)A regulators can modulate non-coding RNAs via multiple mechanisms, including regulation of pri-miRNA processing, affecting m\(^6\)A-dependent ceRNA networks, promoting the nucleation of circRNA, and even by regulating the interaction between IncRNAs and proteins. These studies typically use poly(A)\(^+\) RNA for m\(^6\)A mapping, excluding many regulatory ncRNA species that do not contain poly(A) tails. In addition, miRNA and IncRNA can also regulate m\(^6\)A levels in cancer cells. miRNAs can target the corresponding mRNA of m\(^6\)A regulators, recruiting their nucleation, thus altering m\(^6\)A levels in cancer cells. In the nucleus, IncRNAs may act as scaffolds, providing a platform for other effector molecules to interact with m\(^6\)A. Additionally, IncRNAs may be involved in maintaining the stability of m\(^6\)A-related proteins. Notably, Huang et al.\(^8^6\) reported that circSTAG1 can bind ALKBH5 and inhibit its nucleation, thus changing the total RNA m\(^6\)A modification and increasing the m\(^6\)A modification level of RNAs, including FAAH mRNA in the chronic unpredictable stress mouse hippocampus. This study provides the foundation for analyzing the relationship between circRNA and m\(^6\)A modification. circRNA can not only be modified by m\(^6\)A, but can also regulate the process of m\(^6\)A modification by binding to m\(^6\)A-modified proteins. However, the regulation of m\(^6\)A modification by circRNA has not yet been reported in human cancer.

The crosstalk between non-coding RNAs and m\(^6\)A modifications provides a new perspective for us to study normal development and tumorigenesis and to understand its complex regulatory network. Dynamic m\(^6\)A modification of non-coding RNA represents a novel mechanism to regulate genetic information in cancer cells and adds to our understanding of how m\(^6\)A modifications regulate RNA and downstream biological processes. The finding that m\(^6\)A levels can in turn be regulated by non-coding RNAs enriches our understanding of non-coding RNA molecular networks in cancer progression. Together, these findings provide new directions to study the mechanism of non-coding RNA in tumorigenesis and development.

### Future Prospects

According to the central dogma, generation of the entire proteome from the genome requires regulation at four main stages: RNA production (including epigenetic regulation and transcriptional regulation), RNA degradation, protein production (translation regulation), and protein degradation. Of these, regulation of translation...
constitutes the most important mode of regulation in the cell, accounting for more than half of all regulatory events.\textsuperscript{37} To date, there have been few studies in this field because of the limitations of the current research methods and other factors.

At present, RNA methylation and translation-omics are new directions in epigenetic research and will provide important insights into the novel mechanisms governing normal physiological and abnormal cellular processes. Research on the functional interaction of non-coding RNA and m$\textsuperscript{6}$A modification deserves particular attention. It is worth noting that studies investigating the crosstalk between non-coding RNA and m$\textsuperscript{6}$A regulators typically involve members transcribed from different parental genes. Whether non-coding RNA and m$\textsuperscript{6}$A regulators transcribed from the same gene can interact to regulate downstream target genes through positive or negative feedback loops will be of interest in the future. Studying the cross regulation of non-coding RNA and m$\textsuperscript{6}$A modification will facilitate the discovery of critical targets for the diagnosis and treatment of cancer patients, which is the ultimate goal of personalized medicine. Given the involvement of these regulatory processes in normal development and other diseases, these findings are likely to have widespread applications, although the specific mechanisms in these cell types require further exploration.\textsuperscript{38,39}

**AUTHOR CONTRIBUTIONS**

W.G., W.X., and Y.W. conceived this manuscript. F.D., Y.L., C.A., and L.Z. collected and prepared the related references. F.D., Y.W., and Y.L. drafted the manuscript. Y.G. and F.D. drew the figures. Y.L., L.D., and L.Z. performed data analysis and tabulation. W.G., Y.W., H.L., and W.X. supervised and revised the manuscript. All authors read and approved the final manuscript.

**CONFLICTS OF INTEREST**

The authors declare no competing interests.

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