The role of M\(^6\)A modification in the regulation of tumor-related IncRNAs

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N\(^6\)-methyladenosine (m\(^6\)A) is the most abundant modification in eukaryotic cells, and it regulates RNA transcription, processing, splicing, degradation, and translation. Long non-coding RNAs (lncRNAs), as transcriptional products with no or limited protein coding ability more than 200 nt in length, play an important role in epigenetic modification, mRNA transcription, splicing, stability, translation, and other biological functions. Extensive studies have shown that both m\(^6\)A modification and lncRNAs are involved in the pathogenesis of various diseases, such as kinds of cancers, heart failure, Alzheimer’s disease, periodontitis, human abdominal aortic aneurysm, and obesity. There are many mechanisms of both m\(^6\)A modification and lncRNA that have not been elucidated. In this review, we summarize the role of m\(^6\)A modification in the regulation of tumor-related lncRNAs. We also discuss the potential applications and possible future directions in this field.

BACKGROUND

Long non-coding RNAs (lncRNAs) are novel ncRNAs longer than 200 nt and generally transcribed in the human genome.1 It is now confirmed that lncRNAs play a significant role in biological functions such as epigenetic modification, mRNA transcription, splicing, stability, and translation.2 Specifically, it has been demonstrated that lncRNA is involved in the occurrence, development, and prognosis of various diseases, including carcinomas,3–5 carcinomas,3–5 neuropsychiatric disorders,5,6 immune molecular mechanism,6–10 and cardiac gene programs.11 lncRNAs can interact with proteins, RNA, DNA, and can mediate their function.10 However, there are limited studies to show how lncRNAs are regulated.

Thus far, numerous studies on methylation modification in eukaryotic cells have shown that many methylation modifications can regulate RNA in eukaryotic cells, including 7-methylguanin (m\(^7\)G), 5-methylcytosine (m\(^5\)C), N6,2’-O-dimethyladenosine (m\(^2\)Am), N\(^\beta\)-methyladenosine (m\(^\beta\)A), 5-hydroxymethylcytosine (5hmC), and N6-methyladenosine, among others.12 One of the most abundant modification methods in RNAs has been shown to be m\(^6\)A. Studies have demonstrated that the m\(^6\)A modification is dynamic and reversible, and it can influence the metabolism of mRNA and regulate RNA transcription, export, splicing, degradation, and translation.13 The m\(^6\)A methylation level is related to the occurrence and progression of many diseases, such as tumors,14–17 heart failure,16 Alzheimer’s disease,19 periodontitis,20 human abdominal aortic aneurysm,21 and obesity.22 However, the mechanism of how cell-specific m\(^6\)A methylomes are established is poorly described.23

There are many mechanisms of both m\(^6\)A modification and lncRNA that have not been elucidated. In this review, we summarize the role of m\(^6\)A modification in the regulation of tumor-related lncRNAs. We also discuss the potential applications and possible future directions in this field.

m\(^6\)A WRITERS, READERS, AND ERASERS

m\(^6\)A has modifications and effects on RNA through the dynamic interaction between three homologous factors, writers (methyltransferases), readers (binding proteins), and erasers (demethylases)24 (Figure 1).

Writers

An m\(^6\)A writer is a protein complex with a high molecular weight of around 1 MDa,25 which consists of the following core subunits: methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and their cofactors; Wilms tumor 1-associating protein (WTAP); Vir like m\(^6\)A methyltransferase associated (VIRMA); zinc finger CCCH-type containing 13 (ZC3H13); CBLL1 (also known as HAKAI); RNA-binding motif protein 15/15B (RBM15/15B); and the complex methylate mRNAs in a sequence context of RRACH (R = A or G; H = A, C, or U),26 often in 30 UTRs.27 Methyltransferase-like 16 (METTL16) is a novel m\(^6\)A writer protein when we exclude the above-mentioned complex, m\(^6\)A methyltransferase complex (MTC).27 METTL3, as a significant catalytic subunit of MTC that

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mett14 as the second methyltransferase loci in RNAs. In addition to MTC, METTL16 is an independent enzyme of m6A methylation modification. METTL14 could form a stable heterodimer with METTL3. At the same time, METTL14 plays a key role in β cell survival, insulin secretion, and glucose homeostasis. Knockdown of METTL14 could downregulate the m6A level in both the nucleus and cytoplasm. Hence, we can conclude that METTL3 plays an important role in m6A regulation. As a great adaptor needed to assist METTL3 activity, METTL14 has homology to methyltransferases. METTL14 could form a stable heterodimer core complex with METTL3. At the same time, METTL14 plays a key role in β cell survival, insulin secretion, and glucose homeostasis. Knockdown of METTL14 could downregulate the m6A level of X-inactive specific transcript (XIST) and augment XIST expression. We can regard METTL14 as the second methyltransferase enzyme. WTAP is also a pivotal component of MTC, associated with the tumor suppressor gene Wilms’ tumor 1, recruiting METTL3 and METTL14 to be localized in mRNA targets to catalyze m6A methylation together. Depletion of WTAP could induce a loss of nuclear speckle localization for METTL3 and METTL14. VIRMA was originally known as KIAA1429, a recently identified component of MTC, which has been proven to mediate the deposition of preferential m6A modification. VIRMA could recognize the m6A writer and then have different functions on mRNA. Erasers are proteins that can regulate the process of demethylation, including FTO, ALKBH5, ALKBH9, and ALKBH10B.

Readers
m6A readers are a type of binding proteins that can specifically decode the m6A mark and affect methylated mRNAs. In addition, different m6A readers have different functions on mRNA. One class of abundant m6A readers belongs to the YTH family. YTHDF1–3, YTHDC1–2, IGF2BPs, HNRNPs, eIF3, FMRP, PRRC2A, METTL3, and LRPPRC could recognize the m6A writer and then have different functions on mRNA. Furthermore, RNA-binding protein YTHDF3 proteins could accelerate protein synthesis with mRNA as well as degrading both tumor promoter and suppressor gene mRNAs.[34,37] YTHDF3 could accelerate protein synthesis with YTHDF1 and mediate the decay of methylated mRNA through YTHDF2.[38] Recent research elucidated that YTHDF3 proteins could limit HIV infection of new target cells at the period of reverse transcription. YTHDC1 localizes to the nucleus in cultured mammalian somatic cells, while YTHDC2 is meiotic spermatocytes’ cytoplasmic. YTHDC1 was confirmed to modulate mRNA splice site selection in a concentration-dependent manner through minigene reporter assays.[51] As the largest member of the YTH family, YTHDC2 also binds m6A preferentially within the consensus motif, and it can enhance the translation efficiency while decreasing the abundance of its target mRNAs.[39] Huang et al.[41] reported that insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs; including IGF2BP1/2/3) are another species of m6A readers in post-transcriptional gene regulation and cancer biology. IGF2BPs have the function of stabilizing target mRNA and promoting their translation level in an m6A-dependent manner and can then affect gene expression.[42,43] Several heterogeneous nuclear ribonucleoproteins (HNRNPs), including HNRNPC, HNRNPG, and HNRNPA2/B1, regulate alternative splicing (AS) or processing of target transcripts. HNRNPC could affect precursor (pre-)mRNA stability, splicing, export, and translation via binding to nascent RNA transcripts.[44] Zhou et al.[45] showed that HNRNPG could regulate AS through interacting with m6A-modified embryonic pre-mRNA and the phosphorylated C-terminal domain of RNA polymerase II. Moreover, through bioinformatics analysis, Wu et al.[46] suggested that HNRNPA2/B1 may modulate the effects of m6A via an “m6A switch” mechanism, rather than acting as a direct m6A reader. Eukaryotic initiation factor 3 (eIF3) plays a role in the translation process, including the recognition of the start codon and the recruitment of ribosomes to the mRNA. eIF3 is a complex of nine subunits, among which eIF3G has been shown to be involved in m6A-mediated translation repression. eIF3G associates with the m6A reader YTHDF2, which enhances the binding of eIF3G to m6A-modified mRNAs, leading to the repression of translation.

Figure 1. m6A writer complex is conducted by METTL3, METTL14, WTAP, RBM15, ZC3H13, VIRMA, and CBLL1
Additionally, METTL16 is another novel independent RNA methyltransferase. Readers such as YTHDF1–3, YTHDC1–2, IGF2BPs, HNRNPs, eIF3, FMRP, PRRC2A, METTL3, and LRPPRC could recognize the m6A writer and then have different functions on mRNA.
(eIF3) also serves as a reader of m^6^A and binds a single 5’ UTR m^6^A directly rather than 5’ cap to promote translation under cellular stresses. Fragile X mental retardation protein (FMRP) can directly bind YTHDF2 and indirectly maintain m^6^A-containing mRNAs instead of recruiting RNA-binding proteins (RBPs). Hsu et al. concluded that FMRP might affect the nuclear export of m^6^A-modified RNA targets. Recently, Wu et al. identified proline rich coiled-coil 2A (Prrc2a) as a novel m^6^A reader regulating oligodendrocytes expression. Apart from the above readers, METTL3 can act as an m^6^A reader as well, enhancing translation by binding a small part of cytoplasmic m^6^A-modified mRNA. In addition, researchers have identified leucine-rich pentatricopeptide repeat-containing protein (LRPRRC) as a potential reader.

**Erasers**

m^6^A regulation depends on the readers, including fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5), to catalyze the demethylation of m^6^A. FTO, also known as AlkB homolog 9 (ALKBH9), was discovered as the first m^6^A eraser that established the dynamic and reversible m^6^A modification. FTO localizes largely in the nucleus and mediates 5%–10% of total mRNA m^6^A demethylation; however, FTO is also highly abundant in the cytoplasm of certain leukemia cells and can mediate up to 40% of all mRNA m^6^A. Yang et al. suggested that knockdown of FTO increases m^6^A methylation in the key pro-tumorigenic melanoma cell-intrinsic genes, which resulted in the increase of RNA decay through the m^6^A reader YTHDF2. Nevertheless, whether FTO recognizes and removes m^6^A from the internal m^6^A motifs is still an essential problem. Unlike FTO, ALKBH5 catalyzes m^6^A progression directly by removing the methyl group from m^6^A-methylated adenosine instead of oxidative demethylation. ALKBH5 inhibits the binding of reader protein YTHDF2 in placenta variant translocation 1 (PVT1) by down-regulating the m^6^A modification of PVT1. Additionally, ALKBH5 deficiency boosts PDAC cell proliferation, migration, and invasion both in vivo and in vitro. ALKBH5 was also involved in glioblastoma, and it plays a key role in spermatogenesis and male fertility. ALKBH5 is an FTO homolog that ensures the equilibrium of m^6^A modification in the transcriptome. In addition to the two erasers, *Arabidopsis* is an m^6^A demethylase of mRNA, which affects the transformation of *Arabidopsis thaliana* from vegetative growth to reproductive growth and its mRNA stability.

**CHARACTERISTICS, REGULATORY MECHANISMS, AND BIOLOGICAL FUNCTIONS OF lncRNAs**

lncRNAs are defined as a class of non-coding RNAs greater than 200 nt in length, which lack an open reading frame (ORF) and are unable to encode protein. lncRNAs have been detected in all species at the genomic level, including animals, plants, fungi, prokaryotes, and even viruses. Interestingly, only less than 2% of the genomic sequence is transcribed into mRNA, which suggests that the precise function of ncRNAs needs greater in-depth exploration. Many lncRNAs undergo the same RNA processing steps as mRNAs, including splicing and polyadenylation, while they are also transcribed by RNA polymerase II (RNA Pol II). Compared with protein-coding genes, the proportion of conserved specificity is apparently lower in lncRNAs. Similar to microRNAs (miRNAs), a type of small ncRNAs, lncRNAs have been calculated to have a high degree of tissue specificity in humans. Testis differs from other tissues in that it has great tissue-specific lncRNAs. Different levels of expression in different tissues suggest that specific lncRNAs can serve as biomarkers for diseases, especially cancer (Table 1).

The growing ranks of lncRNAs have attracted adequate attention on the regulatory mechanisms. Regulation of chromatin structure by histone modification and chromatin remodeling is the most classic mode. Second chromosome locus associated with prostate-1 (SChLAP1) can repress the modulation of the SWI/SNF chromatin remodeling complex to promote invasiveness in human prostate cancer. Additionally, lncRNAs are associated with imprinted gene clusters that can mediate the transcriptional silencing. The writers give an example of how Kcnq1ot1 accumulates on the chromatin of the promoter of the silenced alleles. At the same time, it also plays an inhibitory role in histone modification in mouse placenta, similar to XIST, which is representative of the field in which m^6^A functions. Zhang et al. concluded that UPK1A antisense RNA 1 (UPK1A-AS1) accelerated the cell cycle process and promoted the development of hepatocellular carcinoma (HCC) by interacting with EZH2 and sponging miR-138-5p. lncRNAs are also related to the activation of transcription factors to facilitate gene expression, such as IncKdm2b, and can promote ESC self-renewal via activating Zbtb3. Activation of Zpf292 to maintain the intestinal group 3 innate lymphoid cells (ILC3s) was also a positive effect. Furthermore, studies have shown that enhancer lncRNAs (eRNAs) can upregulate gene expression by interacting with the proximal promoter. lncRNAs also perform specific physiological functions as “miRNA sponges” to bind with miRNAs to protect mRNAs from degradation, suggesting that this posttranscriptional regulation could be a popular therapeutic target for many diseases in the future. For instance, muscle anabolic regulator 1 (MAR1), as a miRNA sponge, decoys miR-487b to form a complementary sequence and release inhibitory effects on Wnt5a. Given that m^6^A is the most abundant modification in mammalian RNA, it has become a research hotspot recently.

Moving forward with research on regulatory mechanisms, several scientists are focusing on the cellular physiologic functions of lncRNAs, including cellular differentiation and development. lncRNAs play critical roles in the disease process, such as different cancers, heart diseases, diabetes, muscle disease, and Alzheimer’s disease, among others. Since lncRNAs are involved in almost all of our lives, more attention to modulation, especially m^6^A, is reasonable.

**ROLE OF m^6^A METHYLATION IN THE REGULATION OF TUMOR-RELATED lncRNAs**

To date, especially in the last 5 years, studies on m^6^A methylation modification keep emerging, and great progress has been made. Although recent studies have shown that abnormal regulation of m^6^A can lead to various diseases, especially in some tumors, the
The role of m6A modification in tumorigenesis and tumor suppression is being gradually explored by scientists. m6A methylation could regulate almost all RNA metabolism steps by certain factors and proteins, including writers, readers, and erasers. Despite the advances made, m6A-modified ncRNAs remain to be further investigated. Our research group mainly focuses on m6A methylation modification and IncRNAs; hence, we summarize the role of m6A modification in the regulation and function of IncRNAs (Figure 2).

**m6A modification regulates IncRNAs**

m6A modification may affect IncRNA function through a variety of regulatory mechanisms (Figure 3).

On the one hand, m6A modification acts on the RNA-DNA triple helix structure to regulate the relationship between IncRNAs and specific DNA sites. On the other hand, m6A modification provides binding sites for readers or regulates the structure of local RNA, and then induces the binding of RBPs to regulate the function of IncRNAs.117

m6A writers could modulate IncRNAs; for instance, XIST is a target of RBM15/15B-directed methylation,72 which interacts with the m6A machinery directly via ZC3H13.118 Proteomic analysis showed that WTAP is an XIST-related protein, and RBM15/RBM15B also bind to METTL3 in a WTAP-dependent manner to act on XIST as an m6A methylase complex, thereby affecting its function.77 Both METTL16 and METTL3 are also recruited to IncRNAs, including the well-studied MALAT1 and XIST.119 Deleting the m6A domain in XIST and analysis of these genes will immediately have affects downstream, suggesting that m6A’s role in XIST is far less significant than when the cell-scope system is destroyed and the entire cellular transcription level used to analyze gene expression is analyzed.109

Xue et al.120 identified that m6A modification was installed on METTL3 to enhance the stability of the ABHD11-AS1 transcript, thereby increasing its expression, which emphasizes the function and mechanism of METTL3-induced ABHD11-AS1 in non-small cell lung cancer (NSCLC). As a critical factor sustaining m6A levels in prostate cancer cells, VIRMA downregulation reduces the stability and abundance of oncogenic IncRNAs and the invasive phenotype of prostate cancer by attenuating the overall level of m6A.121

m6A readers also have such a functional role in IncRNAs. YTHDC2 is located in the nucleus and cytoplasm and has been shown to bind to the selective m6A sites in IncRNAs.72 HNRNPC and HNRNP2/B1 are proteins that bind to m6A sites after local and secondary structural changes of IncRNA.122 A novel IncRNA (DMDRMR) that regulates DNA methylation and cooperates with an RNA m6A reader promotes tumor growth and metastasis in clear cell renal cell carcinoma (ccRCC). Gao et al.123 elucidated that DMDRMR interacted with IGF2BP3 to regulate target genes in an m6A-dependent manner and might be a potential diagnostic, prognostic, and therapeutic target for ccRCC. As a nuclear m6A reader, YTHDC2 could regulate RNA splicing, and in gynecologic tumor cell lines, hypoxia leads to a decrease in YTHDC1 protein levels by altering splicing to produce meaninglessly mediated decay of targeted mRNA subtypes.124 At the same time, Hu et al.125 indicated that IGF2BP2 could promote pancreatic cancer cell proliferation and stemness-like properties as an m6A reader through regulating its novel target lncRNA DANCR stability. Yoneda et al.126 suggested that under the m6A modification, promoter-associated ncRNA (pncRNA)-D, an irradiation-induced

| Table 1. lncRNA biomarkers in cancers |
|-------------------------------------|
| Cancer                | lncRNA biomarker | Expression | References |
|------------------------|-----------------|------------|------------|
| Breast cancer          | HOTAIR          | up         | 78         |
|                        | H19             | up         | 79         |
|                        | LSNINCT5        | up         | 79         |
|                        | NEAT1           | up         | 79         |
| Lung cancer            | SOX2-OT         | up         | 80         |
|                        | ENSG0000245648  | up         | 80         |
|                        | MALAT1          | up         | 80         |
|                        | HOTAIR          | up         | 81         |
|                        | TUG1            | down       | 81         |
|                        | GAS5            | down       | 82         |
|                        | PVT1            | up         | 83         |
|                        | HOTAIR          | up         | 84         |
| Hepatocellular carcinoma | UCA1           | up         | 85         |
|                        | IncRNA-URHC     | up         | 86         |
| Gastric cancer         | LINC00670       | up         | 87         |
|                        | UCA1            | up         | 88         |
|                        | H19             | up         | 89         |
|                        | LINC00659       | up         | 89         |
| Pancreatic cancer      | H19             | up         | 93         |
|                        | BX111           | up         | 93         |
|                        | GLS-AS          | down       | 93         |
| Colorectal cancer      | UCA1            | up         | 94         |
|                        | MALAT1          | up         | 95         |
|                        | PVT1            | up         | 96         |
|                        | CRNDE           | up         | 97         |
| Prostate cancer        | PCA3            | up         | 98         |
|                        | HOTAIR          | up         | 98         |
|                        | DRAIC           | down       | 98         |
|                        | MALAT-1         | up         | 99         |
| Bladder cancer         | UCA1            | up         | 100        |
|                        | HOTAIR          | up         | 101        |
|                        | GAS5            | up         | 101        |
| Glioma                 | HOUX211-AS      | up         | 102        |
|                        | FOXD1-AS1       | up         | 103        |
|                        | NEAT1           | up         | 104        |
|                        | ANCR            | up         | 105        |
|                        | PCED1B-AS1      | up         | 106        |
|                        | PCED1B          | up         | 106        |
602-nt lncRNA transcribed from the promoter region of the cyclin D1 (CCND1) gene, influences the regulation of CCND1 gene expression and cell cycle progression. As an additional regulatory post-transcriptional process for gene expression, AS could be regulated by m^6^A modification and subsequently generate lncRNAs from one primary transcript.127 Olf29-ps1, a lncRNA pseudogene expressed in myocardial-derived suppressor cells (MDSCs), can be regulated by the inflammatory factor interleukin-6 (IL-6), and it relies mainly on the m^6^A-modified Olf29-ps1/mir-214-3-p/MyD88 regulatory pathway to regulate MDSC immune inhibition and differentiation.128 Zhu et al.129 discovered that LINC00266-1, a previously annotated lncRNA, could encode an uncharacterized peptide, named RNA-binding regulatory peptide (RBRP), which has the ability to combine IGF2BP1 and enhance its ability to recognize m^6^A on RNAs, and subsequently plays a carcinogenic role in tumorigenesis. The combination of METTL3/14 and WATP as a writer, ALKBH5 works as an eraser, and YTHDF1 as a reader all in concert and subsequently generate lncRNAs from one primary transcript, such as m^6^A in lncRNA taurine upregulation 1 (TUG1).134 MALAT1 could also regulate the output of chimeric mRNA in an m^6^A-dependent manner, including YTHDC1 and METTL14, thereby controlling the differentiation of hematopoietic cells.135 Wang et al.136 further revealed that YTHDC1 recognition of MALAT1-m^6^A plays a key role in maintaining the composition of nuclear spots and genomic binding sites, thereby regulating the expression of several key oncogenes, and artificial tethering of YTHDC1 to m^6^A-deficient MALAT1 largely saved the metastatic potential of cancer cells. The Hox transcript antisense intergenic RNA (HOTAIR) is a lncRNA of about 2.2 kb that is transcribed from the antisense strand of the developmental the HOXC antisense gene cluster on chromosome 12, and Meyer et al.137 used methylated RNA immunoprecipitation followed by sequencing (MeRIP-seq) in HEK293T cells and found a single m^6^A peak region (126nt) in the front half of HOTAIR, which did not overlap with m^5^C. Dominissini et al.138 mapped m^6^A to the lncRNAs, for instance, PVT1 and NEAT1 and uncharacterized lncRNA transcripts. Only a few studies have carefully mapped the locations of modified residues in a single transcript, such as m^6^A in lncRNA taurine upregulation 1 (TUG1).134

In addition, m^6^A-modified lncRNA can induce the proliferation, migration, and apoptosis of tumor cells, including pancreatic carcinoma, oophoroma, and hepatoma.139 Wu et al.140 characterized a Y-linked lncRNA, LINC00278, which is downregulated in male ESCC, and smoking could downregulate m^6^A modification of LINC00278 translation. Moreover, their data suggested that METTL3, METTL14, and WTAP work as writers, ALKBH5 works

Therefore, we can combine the two to explore the role and function of m^6^A-modified IncRNA in tumors. Next, we briefly review the relevant research results in this field in recent years.

Analysis of datasets from The Cancer Genome Atlas (TCGA) Research Network acute myeloid leukemia (AML) study showed a solid association between mutations and copy number variation of m^6^A regulatory genes and TP53 in AML patients. Additionally, changes in the m^6^A regulatory gene lead to poor survival in AML patients.124 Importantly, the treated MALAT1 transcript contains a 3’-triple helical RNA stabilization element consisting of a U-rich inner ring associated with a downstream A-rich channel to protect the MALAT1 transcript from degradation. METTL16, one novel m^6^A writer, recognizes and combines this triple helix, which increases the possibility that the m^6^A modification exists in this triple helix.135 Only a small part of MALAT1 molecules (about 2%–3%) carried the m^6^A modification at the other predicted sites (A2674/2684/2698) in two out of four cell lines.134 MALAT1 could also regulate the output of chimeric mRNA in an m^6^A-dependent manner, including YTHDC1 and METTL14, thereby controlling the differentiation of hematopoietic cells.135 Wang et al.136 further revealed that YTHDC1 recognition of MALAT1-m^6^A plays a key role in maintaining the composition of nuclear spots and genomic binding sites, thereby regulating the expression of several key oncogenes, and artificial tethering of YTHDC1 to m^6^A-deficient MALAT1 largely saved the metastatic potential of cancer cells. The Hox transcript antisense intergenic RNA (HOTAIR) is a lncRNA of about 2.2 kb that is transcribed from the antisense strand of the developmental the HOXC gene cluster on chromosome 12, and Meyer et al.137 used methylated RNA immunoprecipitation followed by sequencing (MeRIP-seq) in HEK293T cells and found a single m^6^A peak region (126nt) in the front half of HOTAIR, which did not overlap with m^5^C. Dominissini et al.138 mapped m^6^A to the lncRNAs, for instance, PVT1 and NEAT1 and uncharacterized lncRNA transcripts. Only a few studies have carefully mapped the locations of modified residues in a single transcript, such as m^6^A in lncRNA taurine upregulation 1 (TUG1).134

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as an eraser, and YTHDF1 work as a reader for LINC00278 m6A modification. Sun et al. revealed a novel LINC942-METTL14-CXCR4/CYP1B1 signaling axis, which provides a novel target for the prevention and treatment of breast cancer (BRCA) and a mechanism of crosstalk m6A epigenetic modification. Clinically, Ni et al. suggested that the expression of IncRNA GAS5 in the tumor of colorectal cancer (CRC) patients is negatively correlated with the protein levels of YAP and YTHDF3. Yang et al. identified a “METTL14-YTHDF2-IncRNA” regulating axis in CRC cells that could mediate the degradation of XIST, significantly enhancing the proliferation and invasion ability of CRC cells in vitro and promoting the occurrence and metastasis of tumor in vivo. In clinical research, IncRNA RP11-139J23.1 is highly expressed in CRC, which is controlled by m6A methylation, Wu et al. elucidated that m6A-induced IncRNA RP11 could trigger the metastasis and proliferation of CRC cells by upregulation of Zeb1. Zhu et al. demonstrated that IncRNA KB-1980E6.3 maintains the stemness of breast cancer stem cells through the IncRNA KB-1980E6.3/IGF2BP1/c-Myc axis and suggested that disruption of this axis may provide a new therapeutic target for refractory hypoxic tumors. In addition, Hou et al. suggested that LINC00460 interacts with IGF2BP2 and DHX9 to promote mRNA stability of the high mobility group A1 (HMGA1), a member of non-histone chromatin protein, leading to a biological response to malignant proliferation and widespread metastasis of CRC, and HMGA1 is enhanced by METTL3, while LINC00460 relies on METTL3 to regulate HMGA1 expression. In HCC, METTL3-mediated m6A modification results in the upregulation of LINC00958 by stabilizing its mRNA, and LINC00958 sponges miR-3619-5p to increase the expression of hepatocellular carcinoma-derived growth factor, so as to promote HCC progression and lipogenesis. By regulating IncRNA DANCR expression, IGF2BP2 could work together with DANCR on pancreatic cancer cell proliferation and

Figure 3. m6A modification regulates IncRNA through various regulatory mechanisms, and it plays different roles in the nucleus, cytoplasm, and extracellular cells.
tumorigenesis. He et al. revealed that ALKBH5 could inhibit pancreatic cancer by demethylation of lncRNA KCNK15-AS1 and regulating its expression, and this new mechanism identified a potential pancreatic cancer therapeutic target. Furthermore, Chen et al. found that ALKBH5 can decrease the m6A modification of PVT1. Thus, the binding of YTHDF2 in PVT1 is inhibited, which promotes the proliferation of osteosarcoma cells and tumor growth. FAM225A is one of the most highly upregulated lncRNAs in nasopharyngeal carcinogenesis (NPC); Zheng et al. found that m6A modification in FAM225A improves its transcripts stability, which may be partly responsible for the significant upregulation of FAM225A in NPC. Ban et al. indicated that LNCAROD, which is overexpressed in head and neck squamous cell carcinoma (HNSCC), is stabilized by m6A methylation and promotes cancer progression via forming a ternary complex with HSPA1A and YBX1 in HNSCC. Wen et al. found that m6A on ncRNA NEAT1-1 plays a key role in regulating RNA Pol II Ser2 phosphorylation and may be a new specific target for the treatment and diagnosis of bone metastatic cancer, and they
think that the novel complex cyclin L1/CDK19/NEAT1-1 may pro-
vide new insights into the underlying mechanism of the pathogenesis
and progression of bone metastatic prostate cancer. Wang et al. investigated that m^A enhances the stability of RHPN1-AS1 methyl-
ated transcript by reducing RNA degradation, leading to upregulation of RHPN1-AS1 in epithelial ovarian cancer. Shen et al. had a
conclusion that YTHDF2-mediated degradation of lncRNA FENDRR promotes cell proliferation by increasing SOX4 expression in endo-
metrioid endometrial carcinoma.

APPLICATIONS AND FUTURE DIRECTIONS
Detailed studies of the distribution and function of chemical modifi-
cations in lncRNAs, as well as their association with related proteins,
will contribute to a comprehensive understanding of the multi-layer
gene expression control mechanisms active in mammalian cells.

Recent technological breakthroughs have rekindled enthusiasm for the study of m^A methylation with some ground-breaking discov-
eries. These allowed for scientists to designate in vivo m^A modifica-
tion events and their association with disease status as functional
associations. Recent investigations have emphasized that m^A modi-
fication has strong and fine-grained control over cell development
programs and can facilitate appropriate, rapid, and complex re-
sponses to developmental cues.

Many lncRNAs are gradually recognized as key factors of virus-host interaction mainly through antiviral response-dependent and anti-
viral response-independent approaches. In contrast, the role of lncRNA in viral infection and innate antiviral response is still un-
clear. Li and Meng concluded that the identification of immune-
related lncRNAs may provide a new direction for the study of the molecular mechanism and treatment of low-grade glioma. Just
because of the role of lncRNAs, we can deduce that m^A-modified lncRNAs can act on immunity. Nevertheless, the biological functions
of m^A modification in immune-related lncRNAs are still unknown,
and thus there is a need for future studies addressing lncRNAs and
immunity.

Although we have made great progress in understanding the function and regulation of m^A modification, there is still much more research
to be done, such as how m^A precisely regulates gene expression. The potential role of m^A and lncRNA modifications in chromatin state
formation may provide additional mechanisms to explain how these modifications are involved in gene regulation during development.

By continuously improving m^A’s detection methods, identifying more readers, writers, and erasers, and discovering the potential func-
tions of m^A, with the joint efforts of many researchers, we will
undoubtedly expand our understanding of m^A’s biological charac-
teristics and of human health and disease. Exploring the role of m^A-modified lncRNAs in tumors will provide a broad prospect for early
detection, prevention, and tumor treatment. For a long time, scholars have devoted more efforts to elucidate the downstream
mechanisms of lncRNAs differentially expressed in tumors, while
their upstream regulation mechanisms have not attracted much
attention. For lncRNAs regulated by m^A modification, m^A modification may be one of the upstream regulatory mechanisms. For the
different expressed lncRNAs regulated by m^A in tumors, we may
try to intervene in the expression level of lncRNAs by using m^A in-
hibitors or activators except small interfering RNA (siRNA) or CRISPR-CAS9 RNA editing, which may be a novel way to regulate
different expressed lncRNAs to even treat tumors.

Further studies on m^A methylated lncRNAs will help us to better un-
derstand their roles in hepatic diseases or other diseases, especially in
tumors. m^A methylated lncRNAs serve as potent prognostic bio-
markers and provide useful individual treatments.

CONCLUSIONS
Two novel developed high-throughput deep-sequencing techniques, MeRIP-seq and m^A sequencing, played a key role in revealing the
functional significance of m^A modification. With scientific tech-
nological development, increasing numbers of m^A-modified lncRNAs will be found and tested.

Additionally, the study of m^A-related proteins and their inhibitors
provides new opportunities for early diagnosis, effective treatment,
and even disease prognosis of cancer, especially when applied in com-
bination with rising immunotherapies. Therefore, further molecular interactions and mechanisms need to be explored. By continuously
improving detection methods, identifying more m^A readers, writers,
and erasers, and discovering m^A-modified lncRNA potential func-
tions, we will undoubtedly expand our knowledge of the contribution
of m^A to human health and disease and its role of in the regulation of
lncRNAs, including molecular pathways and tumorigenesis.

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AUTHOR CONTRIBUTIONS
Y.L. wrote the manuscript and created the figures. B.L. and H.G. re-
viewed and made significant revisions to the manuscript. Y.L.
collected and prepared the related papers. All authors read and
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DECLARATION OF INTERESTS
The authors declare no competing interests.

REFERENCES
1. Xu, J., Bai, J., Zhang, X., Lv, Y., Gong, Y., Liu, L., Zhao, H., Yu, F., Ping, Y., Zhang, G., et al. (2017). A comprehensive overview of lncRNA annotation resources. Brief. Bioinform. 18, 236–249.
2. Pacholewska, A., and Sung, M.H. (2019). lncRNA expression predicts mRNA abundance. Epigenomics 11, 1121–1128.
15. Miao, W., Chen, J., Jia, L., Ma, J., and Song, D. (2019). The m6A methyltransferase METTL3 promotes osteosarcoma progression by regulating the m6A level of LEF1. Mol. Cancer 18, 156.

16. Ni, W., Yao, S., Zhou, Y., Liu, Y., Huang, P., Zhou, A., Liu, J., Che, L., and Li, J. (2019). Identification of IncRNA biomarkers in lung squamous cell carcinoma using comprehensive analysis of IncRNA mediated ceRNA network. Artif. Cells Nanomed. Biotechnol. 47, 3246–3258.

17. Song, L., Zhang, S., Duan, C., Ma, S., Hussain, S., Wei, L., and Chu, M. (2019). Genome-wide identification of IncRNAs as novel prognostic biomarkers of glioma. J. Cell. Biochem. 120, 19518–19528.

18. Zimmer-Bensch, G. (2019). Emerging roles of long non-coding RNAs as drivers of brain evolution. Cells 8, 1399.

19. Elling, B., Chan, J., and Fitzgerald, K.A. (2016). Emerging role of long noncoding RNAs as regulators of innate immune cell development and inflammatory gene expression. Eur. J. Immunol. 46, 504–512.

20. Lin, X., and Meng, Y. (2019). Survival analysis of immune-related IncRNA in low-grade glioma. BMC Cancer 19, 813.

21. Robinson, E.K., Covarrubias, S., and Carpenter, S. (2020). The who and why of IncRNA function: An innate immune perspective. Biochim. Biophys. Acta. Genet. Regul. Mech. 1863, 194419.

22. He, Y., Xing, J., Wang, S., Xin, S., Han, Y., and Zhang, J. (2019). Increased m6A methylation level is associated with the progression of human abdominal aortic aneurysm. Ann. Transl. Med. 7, 797.

23. Chen, F., Li, Z., Deng, C., and Yan, H. (2019). Integration analysis for novel lncRNA markers predicting tumor recurrence in human colon adenocarcinoma. J. Transl. Med. 17, 299.

24. Lin, T., Li, H., Zhang, D., Xu, L., Liu, H., Hao, X., Yan, X., Liao, H., Chen, X., Xie, K., et al. (2019). KIAA1429 contributes to liver cancer progression through N6-methyladenosine-dependent post-transcriptional modification of GATA3. Mol. Cancer 18, 186.

25. Li, R., Yang, Y.E., Jin, J., Zhang, M.Y., Liu, X., Liu, X.X., Yin, Y.H., and Qu, Y.Q. (2019). Identification of IncRNA biomarkers in lung squamous cell carcinoma using comprehensive analysis of IncRNA mediated ceRNA network. Artif. Cells Nanomed. Biotechnol. 47, 3246–3258.

26. Geng, Y., Guan, R., Hong, W., Huang, B., Liu, P., Guo, X., Hu, S., Yu, M., and Hou, B. (2019). The role of N6-methyladenosine (m6A) modification in regulation of RNA methylation writers, readers, and erasers. Mol. Cell 74, 640–650.

27. Pendleton, K.E., Chen, B., Liu, K., Hunter, O.V., Xie, Y., Tu, B.P., and Conrad, N.K. (2017). The U6 snRNA m6A methyltransferase METTL16 regulates SAM synthetase intron retention. Cell 169, 824–835.e14.

28. Warda, A.S., Kretschmer, J., Hackert, P., Lenz, C., Urlaub, H., Höffartner, C., Sloan, K.E., and Bohnsack, M.T. (2017). Human METTL16 is a N6-methyladenosine (m6A) methyltransferase that targets pre-mRNAs and various non-coding RNAs. EMBO Rep. 18, 2004–2014.

29. Zheng, W., Dong, X., Zhao, Y., Wang, S., Jiang, H., Zhang, M., Zheng, X., and Gu, M. (2019). Multiple functions and mechanisms underlying the role of METTL13 in human cancers. Front. Oncol. 9, 1403.

30. Wang, J., Tan, S., Lu, H., Wang, S., and Xu, D. (2019). METTL3 attenuates LPS-induced inflammatory response in macrophages via NF-κB signaling pathway. Mediators Inflamm. 2019, 1320391.

31. Cao, G., Li, H.B., Yin, Z., and Harrell, R.A. (2016). Recent advances in dynamic m6A RNA modification. Open Biol. 6, 160003.

32. Chen, T., Hao, Y.J., Zhang, Y., Li, M.M., Wang, M., Han, W., Wu, Y., Lv, Y., Hao, J., Wang, L., et al. (2015). m6A RNA methylation is regulated by microRNAs and promoters reprogramming to pluripotency. Cell Stem Cell 16, 289–301.

33. Meyer, K.D., and Jaffrey, S.R. (2017). Rethinking m6A readers, writers, and erasers. Annu. Rev. Cell Dev. Biol. 33, 319–342.

34. Li, J., Yue, Y., Han, D., Wang, X., Fu, Y., Zhang, L., Jia, G., Yu, M., Lu, Z., Deng, X., et al. (2014). A METTL3-METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. Nat. Chem. Biol. 10, 93–95.

35. Zhang, L., Xue, Z., Yan, J., Wang, J., Liu, Q., and Jiang, H. (2019). IncRNA Riken-201 and Riken-203 modulates neural development by regulating the Sox6 through sequestering miRNAs. Cell Proli. 52, e12573.

36. Yang, X., Zhang, S., He, C., Xue, P., Zhang, L., He, Z., Zhang, L., Feng, B., Sun, J., and Zheng, M. (2020). METTL14 suppresses proliferation and metastasis of colorectal cancer by down-regulating oncogenic long-non-coding RNA XIST. Mol. Cancer 19, 46.

37. Chen, Y., Lin, Y., Shu, Y., He, J., and Gao, W. (2020). Interaction between N6-methyladenosine (m6A) modification and noncoding RNAs in cancer. Mol. Cancer 19, 94.

38. Ping, X.L., Sun, B.F., Wang, L., Xiao, W., Yang, X., Wang, W.J., Adhikari, S., Shi, Y., Lv, Y., Chen, Y.S., et al. (2014). Mammalian WTP1 is a regulatory subunit of the RNA N6-methyladenosine methyltransferase. Cell Res. 24, 3120391.

39. Hu, Y., Ouyang, Z., Sui, X., Rui, M., Li, H., Gao, Y., Cao, Q., Lu, Q., Zhou, S., et al. (2020). Oocyte competence is maintained by mRNA m6A modification. EMBO J. 39, e12573.

40. Knuckles, P., Lence, T., Haussmann, I.U., Jacob, D., Kreim, N., Carl, S.H., Masiello, K.E., and Bohnsack, M.T. (2017). Human METTL16 is a N6-methyladenosine (m6A) methyltransferase that targets pre-mRNAs and various non-coding RNAs. EMBO Rep. 18, 2004–2014.

41. Zhang, X., Chen, J., and Du, B. (2019). Novel positioning from obesity to cancer: FTO, an m6A RNA demethylase, regulates tumour progression. J. Cancer Res. Clin. Oncol. 145, 19–29.
100. Wieczorek, E., and Reszka, E. (2018). mRNA, microRNA and lncRNA as novel biomarker for diagnosis and prognosis of hepatocellular carcinoma. J. Int. Med. Res. 46, 348–356.

101. Wang, Q., Zhang, J., Liu, Y., Chen, H., Fan, C., Wu, D., and Yang, J. (2019). Inhibition of COX2, mPGES-1 and CYP4A by isoliquiritigenin blocks the angiogenic Akt signaling in glioma through cERNA effect of miR-194-5p and IncRNA NEAT1. J. Exp. Clin. Cancer Res. 38, 371.

102. Cheng, C., Dong, Y., Ru, X., Xia, Y., and Ji, Y. (2020). IncRNA ANCR promotes glioma cells invasion, migration, proliferation and inhibits apoptosis via interacting with EZH2 and repressing PTEN expression. Cancer Gene Ther. Published online December 8, 2020. 10.1038/s41417-020-00263-8.

103. Yang, J., Yu, D., Liu, X., Changyong, E., and Yu, S. (2020). IncRNA PCED1B-AS1 activates the proliferation and restricts the apoptosis of glioma through cooperating with miR-194-5p/PCED1B axis. J. Cell. Biochem. 121, 1823–1833.

104. Atala, A. (2014). 4e: The long noncoding RNA SCLALPI promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. J. Urol. 192, 613.

105. Barlow, D.P., and Bartolomei, M.S. (2014). Genomic imprinting in mammals. Cold Spring Harb. Perspect. Biol. 6, a018382.

106. Coker, H., Wei, G., and Brockdorff, N. (2019). m6A modification of non-coding RNA and the control of mammalian gene expression. Biochim. Biophys. Acta. Gene Regul. Mech. 1862, 310–318.

107. Zhang, D.Y., Sun, Q.C., Zou, X.J., Song, Y., Li, W.W., Guo, Z.Q., Liu, S.S., Liu, L., and Wu, D.H. (2020). Long noncoding RNA UPK1A1:AS indicates poor prognosis of hepatocellular carcinoma and promotes cell proliferation through interaction with EZH2. J. Exp. Clin. Cancer Res. 39, 229.

108. Ye, B., Liu, B., Yang, L., Zhu, X., Zhang, D., Wu, W., Zhu, P., Du, Y., Wu, J., Qin, X., Chen, R., et al. (2017). Long noncoding RNA IncKdm2b is required for LLC3 maintenance by initiation of Zip92spireation. Nat. Immunol. 18, 499–508.

109. Öröm, U.A., Derrien, T., Béringer, M., Gumireddy, K., Gardini, A., Bussotti, G., Lai, F., Zytnicki, M., Notredame, C., Huang, Q., et al. (2010). Long noncoding RNAs with enhancer-like function in human cells. Cell 141, 46–58.

110. Boon, R.A., Jafii, N., Holdt, L., and Dimmeler, S. (2016). Long Noncoding RNAs: From Clinical Genetics to Therapeutic Targets? J. Am. Coll. Cardiol. 67, 1214–1226.

111. Zhang, Z.K., Li, J., Guan, D., Liang, C., Zhuo, Z., Liu, J., Lu, A., Zhang, C., and Zhang, B.T. (2018). A newly identified IncRNA MAR1 acts as a miR-487b sponge to promote skeletal muscle differentiation and regeneration. J. Cachexia Sarcopenia Muscle 9, 613–626.

112. Ouamzain, S., Micheletti, R., Arnan, C., Plaisance, I., Cecchi, D., Schroen, B., Reverter, F., Alexanian, M., Gonzales, C., Ng, S.Y., et al. (2015). CARMEN, a human super enhancer-associated long noncoding RNA controlling cardiac specification, differentiation and homeostasis. J. Mol. Cell. Cardiol. 89 (Pt A), 98–112.

113. Boon, R.A., Jafii, N., Holdt, L., and Dimmeler, S. (2016). Long Noncoding RNAs: From Clinical Genetics to Therapeutic Targets? J. Am. Coll. Cardiol. 67, 1214–1226.

114. Lence, T., Paolantoni, C., Worpenberg, L., and Roignant, J.Y. (2019). Mechanistic insights into m6A RNA enzymes. Biochim. Biophys. Acta. Gene Regul. Mech. 1862, 222–229.

115. Dossin, F., Pinheiro, I., Zylczik, J.J., Roensch, J., Collombet, S., Le Saux, A., Chelmicki, T., Attia, M., Kapoor, V., Zhan, Y., et al. (2020). SPEN integrates transcriptional and epigenetic control of X-inactivation. Nature 578, 455–460.

116. Lui, N., Dai, Q., Zheng, G., He, C., Parisien, M., and Pan, T. (2015). N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518, 560–564.
123. Gu, Y., Niu, S., Wang, Y., Duan, L., Pan, Y., Tong, Z., Zhang, X., Yang, Z., Peng, B., Wang, X., et al. (2021). DMDRM1-mediated regulated modification of m^6^A facilitates CKD progression. Cancer Res. 81, 923–934.

124. Batista, P.J. (2017). The RNA modification N^6^-methyladenosine and its implications in human disease. Genomics Bioinformatics 15, 154–163.

125. Hu, X., Peng, W.X., Zhou, H., Jiang, J., Zhou, X., Huang, D., Mo, Y.Y., and Yang, L. (2020). IGF2BP2 regulates DANC1 by serving as an N6-methyladenosine reader. Cell Death Differ. 27, 1782–1794.

126. Yoneda, R., Ueda, N., Kariyaski, H., Irwaras, M., and Kurokawa, R. (2020). Long noncoding RNA pncRNA-D reduces cyclin D1 gene expression and arrests cell cycle as a m^6^A modification. J. Biol. Chem. 295, 5626–5639.

127. Zha, L.-Y., Zhu, Y.R., Dai, D.J., Wang, X., and Jin, H.C. (2018). Epigenetic regulation of alternative splicing. Am. J. Cancer Res. 8, 2346–2358.

128. Wang, S., Guo, Y., Gao, Y., Cui, Z., and Yang, R. (2019). The pseudogene Olfr29-ps1 promotes the expression function and differentiation of monocytic MDCs. Cancer Immunol. Res. 7, 813–827.

129. Zha, S., Wang, J.Z., Chen, D., He, Y.T., Meng, N., Chen, M., Lu, R.X., Chen, X.H., Zhang, X.L., and Yan, G.R. (2020). An oncoproduct regulates m^6^A recognition by the m^6^A reader IGF2BP1 and tumorigenesis. Nat. Commun. 11, 1685.

130. Banday, A.R., Papenberg, B.W., and Prokunina-Olsson, L. (2020). When the smoke clears m^6^A from a Y chromosome-linked IncRNA, men get an increased risk of cancer. Cancer Res. 80, 2718–2719.

131. Zhang, X., Tu, Q., Xu, Y., Yang, Z., Zhao, W., Zhang, Y., Li, H., and Mi, W. (2020). Dexmedetomidine postconditioning alleviates hypoxia/reoxygenation injury in senescent myocardial cells by regulating IncRNA H19 and m6A modification. Oxid. Med. Cell. Longev. 2020, 9250512.

132. Meng, X., Deng, Y., He, S., Niu, L., and Zha, H. (2021). m^6^A-mediated upregulation of LINC00857 promotes pancreatic cancer tumorigenesis by regulating the miR-150-5p/EF3 axis. Front. Oncol. 11, 629947.

133. Jacob, R., Zander, S., and Gutschner, T. (2017). The dark side of the epitranscriptome: Chemical modifications in long non-coding RNAs. Int. J. Mol. Sci. 18, 2387.

134. Liu, N., Parisien, M., Dai, Q., Zheng, G., He, C., and Pan, T. (2013). Probing N^6^-methyladenosine RNA modification status at single nucleotide resolution in mRNA and long noncoding RNA. RNA 19, 1848–1856.

135. Chen, Z.H., Chen, T.Q., Zeng, Z.C., Wang, D., Han, C., Sun, Y.M., Huang, W., Sun, L.Y., Fang, K., Chen, Y.Q., et al. (2020). Nuclear export of chimeric mRNAs depends on an IncRNA-activated autoregulatory loop in blood malignancies. Cell Death Dis. 11, 566.

136. Wang, X., Liu, C., Zhang, S., Yan, H., Zhang, L., Jiang, A., Liu, Y., Feng, Y., Li, D., Guo, Y., et al. (2021). N^6^-methyladenosine modification of MALAT1 promotes metastasis via reshaping viroarchitecture. Dev. Cell. 56, 702–715.e8.

137. Meyer, K.D., Saletore, Y., Zumbo, P., Elemento, O., Mason, C.E., and Jaffrey, S.R. (2012). Comprehensive analysis of mRNA methylation reveals enrichment in 3' UTRs and near stop codons. Cell 149, 1653–1664.

138. Dominissini, D., Moskitch-Moshkovitz, S., Schwartz, S., Salmon-Divon, M., Ungar, L., Osenberg, S., Cesarkas, K., Jacob-Hirsch, I., Amargolino, N., Kupiec, M., et al. (2012). Topology of the human and mouse m^6^A RNA methylome revealed by m^6^A-seq. Nature 485, 201–206.

139. Xu, K., Sun, Y., Sheng, B., Zheng, Y., Wu, X., and Xu, K. (2019). Role of identified RNA N6-methyladenosine methylation in liver. Anal. Biochem. 578, 45–50.

140. Wu, S., Zhang, L., Deng, J., Guo, B., Li, F., Wang, Y., Wu, R., Zhang, S., Lu, J., and Tao, N. (2020). A novel micropeptide encoded by Y-linked LINC00278 links cigarette smoking and AR signaling in male esophageal squamous cell carcinoma. Cancer Res. 80, 2790–2803.

141. Sun, T., Wu, Z., Wang, X., Wang, Y., Xu, Q., Lin, W., Niu, S., Xu, D., Wu, Y., Chen, Q., et al. (2020). LNC942 promoting METTL14-mediated m^6^A methylation in breast cancer cell proliferation and progression. Oncogene 39, 5358–5372.

142. Wu, Y., Yang, X., Chen, Z., Tian, L., Jiang, G., Chen, F., Li, J., An, P., Lu, L., Luo, N., et al. (2019). m^6^A-induced IncRNA RP11 triggers the dissemination of colorectal cancer via upregulation of Zeb1. Mol. Cancer 18, 87.

143. Zhu, P., He, F., Hou, Y., Tu, G., Li, Q., Jin, T., Zeng, H., Qin, Y., Wan, X., Qiao, Y., et al. (2021). A novel hypoxic long noncoding RNA KB-1980E6.3 maintains breast cancer stem cell stemness via interacting with IGF2BP1 to facilitate c-Myc mRNA stability. Oncogene 40, 1609–1627.

144. Hou, P., Meng, S., Li, M., Lin, T., Chu, S., Li, Z., Zheng, J., Gu, Y., and Bai, J. (2021). LINC00460/DXH9/IGF2BP2 complex promotes colorectal cancer proliferation and metastasis by mediating HMGAl m^6^A mRNA stability on m^6^A modification. J. Exp. Clin. Cancer Res. 40, 52.

145. Rong, D., Dong, Q., Qu, H., Deng, X., Gao, F., Li, F., and Sun, P. (2021). m^6^A-induced LINC00958 promotes breast cancer tumorigenesis via the miR-378a-3p/YY1 axis. Cell Death Discov. 7, 27.

146. He, Y., Hu, H., Wang, Y., Yuan, H., Lu, Z., Wu, P., Liu, D., Tian, L., Yin, J., Jiang, K., and Miao, Y. (2018). ALKBH5 inhibits pancreatic cancer motility by decreasing long non-coding RNA KCNK15-A51 methylation. Cell. Physiol. Biochem. 48, 838–846.

147. Zheng, Z.Q., Li, Z.X., Zhou, G.Q., Lin, L., Zhang, L.L., Lv, J.W., Huang, X.D., Liu, R.Q., Chen, F., He, X.J., et al. (2019). Long noncoding RNA FAM225A promotes nasopharyngeal carcinoma tumorigenesis and metastasis by acting as ceRNA to sponge miR-590-3p/miR-1275 and upregulate ITGB3. Cancer Res. 79, 4612–4626.

148. Ban, Y., Tan, P., Cai, J., Li, J., Hu, M., Zhou, Y., Mei, Y., Tan, Y., Li, X., Zeng, Z., et al. (2020). LNCAROD is stabilized by m^6^A methylation and promotes cancer progression via forming a ternary complex with HSPA1A and YBX1 in head and neck squamous cell carcinoma. Mol. Oncol. 14, 1282–1296.

149. Wen, S., Wei, Y., Zeng, C., Xiong, W., Niu, Y., and Zhao, Y. (2020). Long non-coding RNA NEAT1 promotes bone metastasis of prostate cancer through N6-methyladenosine. Mol. Cancer 19, 171.

150. Wang, J., Ding, W., Xu, Y., Tao, E., Mo, M., Xu, W., Cai, X., Chen, X., Yuan, J., and Wu, X. (2020). Long non-coding RNA RPHN1-A51 promotes tumorigenesis and metastasis of ovarian cancer by acting as cRNA against miR-596 and upregulating LETM1. Aging (Albany NY). 12, 4558–4572.

151. Shen, J., Feng, X.P., Hu, R.B., Wang, H., Wang, Y.L., Qian, J.H., and Zhou, Y.X. (2021). N^6^-methyladenosine reader YTHDF2-mediated long noncoding RNA FENDRR degradation promotes cell proliferation in endometrioid endometrial carcinoma. Lab. Invest., Published online March 10, 2021. https://doi.org/10.1038/s41374-021-00543-3.

152. Maity, A., and Das, B. (2016). N^6^-methyladenosine modification in mRNA: Machinery, function and implications for health and diseases. FEMS J. 283, 1607–1630.