Novel insights into the interplay between m⁶A modification and noncoding RNAs in cancer

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Abstract

N6-methyladenosine (m⁶A) is one of the most common RNA modifications in eukaryotes, mainly in messenger RNA (mRNA). Increasing evidence shows that m⁶A methylation modification acts an essential role in various physiological and pathological bioprocesses. Noncoding RNAs (ncRNAs), including miRNAs, lncRNAs and circRNAs, are known to participate in regulating cell differentiation, angiogenesis, immune response, inflammatory response and carcinogenesis. m⁶A regulators, such as METTL3, ALKBH5 and IGF2BP1 have been reported to execute a m⁶A-dependent modification of ncRNAs involved in carcinogenesis. Meanwhile, ncRNAs can target or modulate m⁶A regulators to influence cancer development. In this review, we provide an insight into the interplay between m⁶A modification and ncRNAs in cancer.

Keywords: Noncoding RNAs, Cancer, m⁶A RNA methylation

Introduction

Up to now, more than 100 kinds of RNA modifications have been confirmed [1]. Among them, m⁶A RNA methylation is one of the most thoroughly studied modifications. m⁶A RNA modification occurs by methylation of the sixth N atom of adenine (A) in mRNAs or ncRNAs [2], m⁶A modification sites tend to be found in the stop codons and 3′-Untranslated region (3′-UTR) of mRNA with a typical consensus sequence RRACH (R = G or A and H = A, C, or U) [3, 4]. Accumulating data show that m⁶A RNA methylation acts by modulating circadian rhythm, gene expression, cell differentiation, stress response, inflammatory response, and carcinogenesis [5–10]. According to the global cancer statistics, there were estimated 18.1 million new cases and 9.6 million deaths in 2018 [11]. Recent studies have shown that m⁶A modification acts a vital role in the diagnosis, treatment and prognosis of cancer patients as well as in carcinogenesis. It also regulates fly sex, virus genome, meiosis of yeast, tissue differentiation, germination, and collateral generation of Arabidopsis [12–15].

Noncoding RNAs (ncRNAs) including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circRNAs (circRNAs) act pivotal roles in cancer [16–18]. m⁶A modification can affect ncRNA splicing and maturation involved in carcinogenesis (Table 1). In this review, we summarize the latest progress about the interplay between m⁶A modification and ncRNAs in cancer.

Molecular compositions of m⁶A RNA methylation

Molecular compositions of m⁶A RNA methylation include m⁶A methyltransferase, m⁶A demethylase, and m⁶A recognition factors (Fig. 1). m⁶A methyltransferases, called “writers” contain methyltransferase-like 3 (METTL3) [19], METTL14 [20], Wilms tumor 1-associated protein (WTAP) [2], KIAA1429 [21], METTL16 [22] and RNA-binding motif protein 15/15B (RBM15/15B) [23]. METTL3 regulates the circadian
Table 1 m^6^A methylation modifies ncRNAs in cancers

| m^6^A component | Related non-coding RNA | Cancer | Function | Role in cancer | Regulation | References |
|------------------|------------------------|--------|----------|----------------|------------|------------|
| METTL3           | miR-25-3p              | PDAC   | Writers  | Oncogene       | Up-regulation | [45]       |
|                  | miR-221, miR-222       | Bladder cancer | Writers  | Oncogene       | Up-regulation | [46]       |
|                  | miR-106b, miR-18a/b, miR-3607, miR-423, miR-30a, miR-320b/d/e | arsenite-induced carcinogenesis | Writers  | Oncogene       | Up-regulation | [47]       |
|                  | miR-1246               | CRC    | Writers  | Oncogene       | Up-regulation | [49]       |
|                  | miR-143-3p             | Lung cancer | Writers  | Oncogene       | Up-regulation | [50]       |
| METTL14          | miR-126                | HCC    | Writers  | Anti-oncogene   | Down-regulation | [48]       |
| METTL3           | IncRNA FAM225A         | NPC    | Writers  | Oncogene       | Up-regulation | [67]       |
|                  | IncRNA LINC00958       | HCC    | Writers  | Oncogene       | Up-regulation | [65]       |
|                  | IncRNA RP11            | CRC    | Writers  | Oncogene       | Up-regulation | [68]       |
|                  | MALAT1                 | NSCLC  | Writers  | Oncogene       | Up-regulation | [69]       |
| METTL14          | XIST                   | CRC    | Writers  | Anti-oncogene   | Down-regulation | [70]       |
| METTL3/METTL14   | LNCAROD                | HNSCC  | Writers  | Oncogene       | Up-regulation | [66]       |
| ALKBH5           | IncRNA NEAT1           | GC     | Erasers  | Oncogene       | Up-regulation | [71]       |
|                  | IncRNA FOXM1-AS        | glioblastoma | Erasers  | Oncogene       | Up-regulation | [57]       |
| YTHDF1           | LINC00278              | ESCC   | Readers  | Anti-oncogene   | Down-regulation | [72]       |
| IGF2BP2          | IncRNA DANCER          | Pancreatic cancer | Readers  | Oncogene       | Up-regulation | [60]       |

**PDAC** pancreatic ductal adenocarcinoma, **HCC** hepatocellular cancer, **NPC** nasopharyngeal cancer, **GC** gastric cancer, **CRC** colorectal cancer, **NSCLC** non-small cell lung cancer, **HNSCC** head and neck squamous cell carcinoma, **ESCC** esophageal squamous cell carcinoma

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**Fig. 1** m^6^A modification is a dynamic and reversible process. m^6^A modification can be executed by "Writers" (METTL3/14, WTAP, KIAA1429, RBM15/15B, METTL16), demethylated by "Erasers" (FTO and ALKBH5) and regulated by "readers" (YTHDF1–3, YTHDC1–2, IGFBP3, eIF3 and HNRNPA2B1)
clock of hepatic lipid metabolism and hematopoiesis [24, 25]. METTL3/14 depletion promotes myeloid differentiation and suppresses the progression of acute myeloid leukemia (AML) [26, 27]. METTL16 maintains the levels of methyl donor S-adenosylmethionine (SAM) [28]. WTAP connects METTL3/14 to form a complex, anchored to the nucleus to catalyze m^6^A methyltransferase [2].

m^6^A methylation is dynamic and can be reversed by m^6^A demethylase, also named as m^6^A “erasers,” containing fat mass and obesity-associated protein (FTO) and alkB homologue 5 (ALKBH5) [29, 30]. FTO shares the motifs with Fe (II)- and 2-oxoglutarate-dependent oxygenase and is related to increased fat mass [31]. FTO harbors an efficient oxidative demethylation activity and reduces the m^6^A levels of mRNAs [30]. ALKBH5 is responsible for RNA splicing and stability and causes the degradation of abnormal transcripts in spermatocytes and round spermatids [32].

m^6^A recognition factors, known as “readers,” consist of YT521-B homology (YTH) domain family (YTHDF1/2/3) [33], YTH domain-containing proteins (YTHDC1/2) [12], heterogeneous nuclear ribonucleoprotein (HNRNP) protein families [33], eucharyotic translation initiation factor 3 (eIF3) [23], and insulin-like growth factor-2 mRNA-binding proteins 1/2/3 (IGF2BP1/2/3) [34]. m^6^A recognition factors act in oligodendrocyte progenitor cells and oligodendrocyte fate [35]. YTHDF1 controls pre-crossing axon guidance in the spinal cord by regulating m^6^A-modified Robo3.1 [36]. HNRNPA2B1 can initiate the immune response to DNA viruses by regulating interferon-α/β and stimulator of interferon genes (STING)-dependent antiviral signaling [37].

m^6^A modification of miRNAs in cancer

As is known to us, the dysregulation of miRNAs is involved in various bio-behaviors, such as mouse prenatal development, immune response, inflammatory response and carcinogenesis [38–41]. METTL3 or HNRNPA2B1 facilitates pri-miRNA processing by recruiting RNA-binding protein DiGeorge syndrome critical region 8 (DGCR8) [42, 43]. METTL3 suppresses osteogenic processes by promoting the maturation of miR-7212-5p and downregulating its target fibroblast growth factor receptor 3 (FGFR3) [44].

Tumor proliferation and tumorigenesis

m^6^A methylation can modify the maturation of miRNAs involved in cell proliferation and tumorigenesis (Fig. 2). miR-25-3p acts as a pivotal role in pancreatic ductal adenocarcinoma (PDAC). Cigarette smoke condensate (CSC) mediates METTL3 to promote miR-25-3p maturation in PDAC tumorigenesis [45]. METTL3 also enhances the binding of pri-miR-221/222 with DGCR8 involved in the proliferation of bladder cancer [46]. m^6^A modification affects arsenite-induced carcinogenesis via modifying multiple miRNAs (miR-106b, miR-18a/b, miR-3607, miR-423, miR-30a, miR-320b/d/e) [47].

Tumor invasion and metastasis

METTL14 promotes the maturation of pri-miR-126 and suppresses the invasion and metastasis of hepatocellular
carcinoma (HCC) [48]. METTL3 facilitates the maturation of pri-miR-1246 to enhance the metastasis of colorectal cancer (CRC) [49]. METTL3 also accelerates the maturation of miR-143-3p, leading to the formation of METTL3/miR-143-3p/vasohibin-1 axis to favor the metastasis of lung cancers [50].

**m6A modification of lncRNAs in cancer**

LncRNAs, a subgroup of non-coding RNAs over 200 nucleotides in length can be modified by m6A methylation in cancer (Fig. 3). m6A methylation facilitates lncRNA X-inactive specific transcript (XIST)-mediated transcriptional repression [51–53]. YTHDC1 preferentially recognizes the m6A residues of XIST and RBM15/15B and participates in XIST-mediated gene silencing [53]. However, RBM15/m6A-MTase complex is reported to act a minor role in XIST-mediated gene silencing [54]. YTHDF2 recognizes m6A methylation site of Inc-Dpf3 to promote its degradation and enhances the binding of Inc-Dpf3 with hypoxia-inducible factor 1-alpha (HIF-1α), leading to the suppression of the glycolysis and migration of dendritic cells [55]. METTL3 can modify metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) to form the METTL3/MALAT1/miR-145/focal adhesion kinase (FAK) axis, contributing to the aggravation of renal fibrogenesis in obstructive nephropathy [56].

**Fig. 3** m6A methylation modifies lncRNAs to participate in tumorigenesis and metastasis in multiple cancers including GSC, HNSCC, NPC, ESCC, lung cancer, GC, HCC, pancreatic cancer and CRC.
Tumor proliferation and tumorigenesis
ALKBH5 has been found upregulated in glioblastoma and prompts the proliferation of glioblastoma stem-like cells (GSCs). A lncRNA antisense to forkhead box M1 (FOXM1-AS) promotes the interaction of ALKBH5 with forkhead box M1 (FOXM1) nascent transcripts to increase FOXM1 expression and GSCs tumorigenesis [57]. LncRNA Differentiation antagonizing non-protein coding RNA (DANCR) contributes to the tumorigenesis of multiple cancers [58, 59]. IGF2BP2 serves as an m^6^A reader to modify DANCR and favors the oncogenicity of pancreatic cancer [60]. MALAT1, the first lncRNA to be found associated with lung cancer, possesses a triple helix structure at its 3’end [61–63]. METTL16 interacts directly with MALAT1 triple helix and promotes cancer cell proliferation [64].

Tumor invasion and metastasis
Long non-coding RNA 00958 (LINC00958) is upregulated by METTL3 and facilitates HCC cell migration and invasion by sponging miR-3619-5p [65]. METTTL3/14 enhance the migration of head and neck squamous cell carcinoma (HNSCC) by upregulating lncRNA activating regulator of DKK1 (LNCAROD) [66]. METTL3-family with sequence similarity 225 member A (FAM225A)-integrin β3 (ITGB3)-FAK/P13K/Akt axis facilitates the metastasis of nasopharyngeal cancer [67]. METTL3 mediates lncRNA RP11–138J23.1 (RP11) or MALAT1-miR-1914-3p-Yes associated protein (YAP) axis to enhance the migration and invasion of CRC and non-small cell lung cancer (NSCLC) [68, 69]. METTTL14 increases the m^6^A levels of XIST and suppresses the invasion of CRC [70]. ALKBH5 favors the invasion and metastasis of gastric cancer (GC) by demethylating lncRNA nuclear parapickle assembly transcript 1 (NEAT1) [71]. YTHD F1 restrains esophageal squamous cell carcinoma (ESCC) by interacting with long intergenic non-protein coding RNA 278 (LINC00278), but ALKBH5 harbors an opposite function [72].

m^6^A modification of circRNAs in cancer
CircRNAs, a novel subset of ncRNAs generated by back-splicing, play a crucial role in protein translation [73]. METTL3 and YTHDC1 are associated with the metabolism of circular RNA zinc finger protein 609 (circ-ZNF609) and promote its production [74]. Minigenes of ribosomes-circRNAs (Ribo-circRNAs) can facilitate protein translation in drosophila heads and circ-ZNF609 boosts protein translation and myoblasts cell proliferation [75, 76]. m^6^A methylation has been reported to affect protein translation of circRNAs [77, 78]. m^6^A motifs are enriched in circRNAs, and a single m^6^A site is regarded as a trigger to initiate the translation of circRNAs. m^6^A regulators are involved in m^6^A-driven protein translation [78]. Mammalian cells can recognize the m^6^A modification on circRNAs to inhibit innate immunity by abrogating immune gene activation and adjuvant activity [79].

In addition, the dysregulation of circRNAs is associated with the progression of multiple cancers, such as breast cancer, gastric cancer (GC), gallbladder cancer and cervical cancer [80–83]. YTHDC1 interacts with circRNA NOP2/Sun RNA methyltransferase 2 (circNSUN2) to facilitate its cytoplasmic export, which leads to colorectal liver metastasis by forming a circNSUN2/IGF2BP2/high mobility group AT-hook 2 (HMGA2) RNA-protein ternary complex in the cytoplasm [84]. m^6^A modification can be involved in the progression of GC by regulating circRNA poliovirus receptor-related 3 (circPVRL3) [85].

m^6^A regulators are regulated by ncRNAs in cancer
LncRNAs have the capabilities to affect m^6^A levels involved in multiple biological processes (Table 2). miRNAs can modulate the binding between METTL3 and its target mRNAs to participate in the reprogramming efficiency of mouse embryonic fibroblasts (MEFs) [86]. miR-149-3p inhibits adipogenesis lineage differentiation and potentiates osteogenic lineage differentiation by targeting FTO [87]. miR-1266 inhibits CRC progression by targeting FTO [88]. miR-145 suppresses the proliferation of HCC by targeting YTHDF2 [89]. Similarly, miR-33a and miR-448 suppress the proliferation of NSCLC by targeting METTL3 and eIF3a [90, 91]. METTL3 is also downregulated by miR-600, which induces the apoptosis of lung cancer [92]. miR-141 suppresses the proliferation of pancreatic cancer by forming the miR-141/IGF2BP2/PI3K/Akt axis [93]. Hepatitis B X-interacting protein (HBXIP) inhibits let-7g expression to upregulate IGF2BP2, thus leading to the formation of a positive feedback loop of HBXIP/let-7g/IGF2BP2/HBXIP to accelerate cell proliferation in breast cancer [94]. miR-497 partially reverses transforming growth factor beta 1 (TGFβ1)-induced epithelial-mesenchymal transition (EMT) and pulmonary fibroblast proliferation through inhibiting eIF3a in alveolar epithelial cells [95].

LncRNAs also regulate m^6^A methylation in cancer. LncRNA derived from hepatocytes (lnc-HC) interacts with HNRNPA2B1 to inhibit cholesterol metabolism in hepatocytes [96]. Long intergenic non-protein coding RNA 470 (LINC00470) interacts with METTL3 to suppress the stability of phosphatase and tensin homolog (PTEN) to facilitate GC progression [97]. LncRNA miR503 host gene (miR503HG) also interacts with HNRNPA2B1 to promote its degradation through an ubiquitin-proteasome pathway in HCC [98]. Similarly, long intergenic non-protein coding RNA 1234
(LINC01234) interacts with HNRNPA2B1 to facilitate cell proliferation and inhibit cell apoptosis in NSCLC [99]. Lin-28 homolog B antisense RNA 1 (LIN28B-AS1) interacts with IGF2BP1 to promote the proliferation and metastasis of lung adenocarcinoma (LUAD) [100]. Long intergenic Noncoding RNA for IGF2BP2 Stability (LINRIS) promotes CRC proliferation by stabilizing IGF2BP2 [101]. The antisense RNA of growth arrest special 5 (GAS5-AS1) depends on ALKBH5 to suppresses the growth and metastasis of cervical cancer [102]. Growth arrest special 5 (GASS) can suppress YAP-mediated YTHDF3 to restrain the proliferative behavior of CRC [103]. Antisense strand of the GATA binding protein 3 gene (GATA3-AS) enhances the interaction between KIAA1429 and GATA binding protein 3 (GATA3) pre-mRNA, leading to the formation of the GATA3-AS/KIAA1429/GATA3 axis in HCC [104].

Clinical application of m⁶A methylation in cancer

m⁶A methylation serves as new biomarkers for diagnosis and prognosis in cancer. m⁶A regulators METTL3, YTHDC2 and HNRNPC are used to predict the prognosis in patients with HNSCC [105]. Upregulated METTL3/FTO or downregulated YTHDF2 and METTL14 can indicate a poor survival in GC, CRC, and HCC [48, 70, 106]. Low expression of METTL14 is associated with tumor differentiation, clinical stage, and microvascular invasion [48]. Low expression of ALKBH5 or FTO predicts an unfavorable marker in lung cancer and HCC [107, 108]. IGF2BP2 is considered as a prognostic marker in pancreatic cancer, esophagogastric junction adenocarcinoma and CRC [60, 109, 110].

m⁶A methylation also participates in drug resistance and cancer treatment. METTL3 stabilizes YAP and Rho GTPase activating protein 5 (ARHGAP5) to induce cisplatin resistance in NSCLC and in GC [69, 111]. HNRNPA2B1 is overexpressed in tamoxifen-resistant breast cancer and reduces 4-hydroxytamoxifen sensitivity [112]. In addition to METTL3 and METTL14, FTO and YTHDF2 are overexpressed in AML [26, 27, 113, 114]. A recent study shows that FTO inhibitor (FB23) and its derivative (FB23–2) promote myeloid differentiation and apoptosis in AML by targeting FTO [115]. m⁶A methylation is also involved in estimating tumor microenvironment and TME infiltration characterization so as to provide insights into an effective immunotherapy for cancer [116]. YTHDF2 is correlated with inflammation infiltration, vascular reconstruction and distant metastasis and predicts a poor prognosis in HCC [117].

In summary, the role of m⁶A modification in clinical application has been widely validated. As for the core members of m⁶A methylation, METTL3/14 exert their functions in many biological processes. METTL3/14 can be regarded as the most important and promising m⁶A regulator and arouse our attention about their modifications on ncRNAs and the clinical application in cancer diagnosis.

Conclusions and perspectives

Accumulating studies have been focused on how m⁶A methylation modifies the stability, splicing and translation of ncRNAs or ncRNAs regulate m⁶A regulators in cancer. The interaction between m⁶A methylation and ncRNAs can impact the different life activities including
cancer cell proliferation, invasion and metastasis. As for the clinical application of m6A methylation, they can be regarded as the potential targets for cancer diagnosis, prognosis and treatment. The latest findings show that lncRNA long intergenic non-protein coding RNA 266–1 (LINC00266–1) interacts with IGF2BP1 by encoding a 71-amino acid peptide, named RNA-binding regulatory peptide, thereby promoting tumorigenesis [118]. However, the specific binding sites between m6A methylation and ncRNAs need be further investigated.

Abbreviations
3′UTR: 3′-untranslated region; ALKBH5: ALK homologue 5; AML: Acute myeloid leukemia; ARHGAP5: Rho GTPase activating protein 5; circRNAs: circular RNAs; circNSUN2: circular RNA NOP2/SUN RNA methyltransferase 2; circPWR3: circular RNA poliovirus receptor-related 3; circ-ZNF609: circular RNA zinc finger protein 609; CRC: Colorectal cancer; CSC: Cigarette smoke condensate; DANCR: Differentiation antagonizing non-protein coding RNA; DGR2B: DiGeorge syndrome critical region 8; elf3: eukaryotic translation initiation factor 3; EMT: Epithelial-mesenchymal transition; ESCC: Esophageal squamous cell carcinoma; FAK: Focal adhesion kinase; FGF3R: Fibroblast growth factor receptor 3; FAM225A: Family with a pseudoparaphilic assembly transcript 1; GATA3: GATA binding protein 3; GATA3-AS: Antisense strand of the GATA kinase; FGFR3: Fibroblast growth factor receptor 3; FAK: Focal adhesion kinase; HCC: Hepatocellular carcinoma; HIF-1α: Hypoxia-inducible factor-1 alpha; HNRF: High mobility group AT-hook 2; HNRP: Heterogeneous nuclear ribonucleoprotein; HNSCC: Head and neck squamous cell carcinoma; IGF2BP1/2/3: Insulin-like growth factor-2 mRNA-binding proteins 1/2/3; ITGβ3: Integrin β3; LINC00266–1: Long intergenic non-protein coding RNA 266–1; LINC00278: Long intergenic non-protein coding RNA 278; LINC00470: Long intergenic non-protein coding RNA 470; LINC00958: Long non-coding RNA 00958; LINC01234: Long intergenic non-protein coding RNA 1234; LINC0228: Lin-28 homolog B antisense RNA 1; LINRIS: Long intergenic non-coding RNA 1; MEFs: Mouse embryonic fibroblasts; METTL3/14/16: Methyltransferase-like 3/14/16; MTA: Myeloid leukemia; MTA1/2/3: YTH domain family 1/2/3; MALAT1: Metastasis-associated lung adenocarcinoma transcript-1; MEFs: Mouse embryonic fibroblasts; METTL13/17: Methyltransferase-like 13/17, long intergenic non-coding RNA; NEAT1: Nuclear RNA long intergenic non-protein coding RNA 266–1 derived from hepatocytes; PiRNAs: Piwi-like RNA; PRC1: Polycomb repressive complex 1; PTEN: Phosphatase and tensin homolog; RBP: RNA-binding protein; WTAP: a regulatory subunit of the RNA N6-methyladenosine methyltransferase. Cell Res. 2014;24:177–89.

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References
1. Boccialetti P, Machnicka MA, Purta E, Pietkowski P, Baginski B, Wiercki T, et al. MODOMICS: a database of RNA modification pathways. 2017 update. Nucleic Acids Res. 2018;46:D303–7.
2. Ping XL, Sun B-F, Wang L, Xiao W, Yang X, Wang W-J, et al. Mammalian WTAP is a regulatory subunit of the RNA N6-methyladenosine methyltransferase. Cell Res. 2014;24:177–89.
3. Dominissini D, Moshitch-Moshkovitz S, Schwartz S, Salmon-Dixon M, Ungermann C, et al. The human mRNA methylome revealed by m6A-seq. Nature. 2012;485:201–6.
4. Meyer KD, Saletore Y, Zumbo P, Clemente O, Mason CE, Jeffery SR. Comprehensive analysis of mRNA methylation reveals enrichment in 3′UTRs and near stop codons. Cell. 2012;149:1635–46.
5. Fustin J-M, Doi M, Yamaguchi Y, Hida H, Nishimura S, Yoshida M, et al. RNA methylation-dependent mRNA processing controls the speed of the circadian clock. Cell. 2013;155:793–806.
6. Zhao BS, Roundtree IA, Heczko P. Post-transcriptional regulation by mRNA modulations. Nat Rev Mol Cell Biol. 2017;18:31–42.
7. Edens BM, Vissers C, Su J, Arumugam S, Xu Z, Shi H, et al. FMK Modules Neural Differentiation through m6A-Dependent mRNA Nuclear Export. Cell Rep. 2019;28:845–854.e5.
8. Engel M, Eggert C, Kaplick PM, Eder M, Köhler S, Tietze L, et al. The Role of m6A/m-RNA Methylation in Stress Response Regulation. Neuron. 2018;99:389–403.e9.
9. Yu R, Li Q, Feng Z, Cai L, Xu Q. m6A Reader YTHDF3 Regulates LPS-Induced Inflammatory Response. Int J Mol Sci. 2019;20:1233.
10. Chen X-Y, Zhang J, Zhu J-S. The role of m6A RNA methylation in human cancer. Mol Cancer. 2019;18:103.
11. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
12. Haussmann IU, Bodi Z, Sanchez-Moran E, Mongan NP, Archer N, Fray RG, et al. m6A potentiates Sxl alternative pre-mRNA splicing for robust Drosophila sex determination. Nature. 2016;530:301–4.
13. Fleming AM, Nguyen NLB, Burrows CJ. Colocalization of m6A and G-Quadruplex-Forming Sequences in Viral RNA (HIV, Zika, Hepatitis B, and SV40) Suggests Topological Control of Adenosine N6-Methyladenosine. ACS Cent Sci. 2019;5:218–28.
14. Shah JC, Clancy MJ. m6A: a gene that mediates MET and nutritional control of meiosis in Saccharomyces cerevisiae. Mol Cell Biol. 1992;12:1078–86.
15. Zhong S, Li H, Bodi Z, Button J, Vespa L, Herzog M, et al. MTA is an essential factor for myeloid leukemia; MTA1/2/3: YTH domain family 1/2/3; MALAT1: Metastasis-associated lung adenocarcinoma transcript-1; MEFs: Mouse embryonic fibroblasts; METTL3/17: Methyltransferase-like 3/17, long intergenic non-coding RNA; NEAT1: Nuclear paraspeckle assembly transcript 1; NSCLC: Non-small cell lung cancer; PDAC: Pancreatic ductal adenocarcinoma; PTEN: Phosphatase and tensin homolog; RBM15/15B: RNA-binding motif protein 15/15B; Ribon- cRNA: Ribosomes-circRNAs; RPI1: RPI1–138 J23.1; SAM: S-adenosylmethionine; STING: Stimulator of interferon genes; TGFβ1: Transforming growth factor beta 1; WTAP: Wilms tumor 1-associated protein; XIST: X-inactive specific transcript; YAP: Yes associated protein; YTH: YTH2/3-1 homology; YTHDC1/2: YTH domain-containing proteins 1/2; YTHDF1/2/3: YTH domain family 1/2/3

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Authors’ contributions
JZ and JSZ designed this study and YCY drafted the manuscript. YCY and YXC collected the data and conducted the picture processing. JZ revised the paper and all authors read and approved the final manuscript.

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20. Liu J, Yue Y, Han D, Wang X, Fu Y, Zhang L, et al. A METTL3–METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. Nat Chem Biol. 2014;10:93–5.

21. Schwartz S, Mumbach MR, Jovanovic M, Wang T, Maclag K, Bushkin GG, et al. Perturbation of m6A writer reveals two distinct classes of mRNA marks at internal and S’ sites. Cell Rep. 2014;4:284–96.

22. Koh OWQ, Goh YT, Goh WSS. Atlas of quantitative single-base-resolution N6-methyladenine methylomes. Nat Commun. 2019;10:5636.

23. Meyer KD, Jaffrey SR. Rethinking m6A Readers, Writers, and Erasers. Annu Rev Cell Dev Biol. 2017;33:319–42.

24. Zhong X, Ju F, Frazier K, Weng X, Li Y, Cham CM, et al. Circadian Clock Regulation of Hepatic Lipid Metabolism by Modulation of m6A mRNA Methylation. Cell Rep. 2018;25:1816–1826.e4.

25. Cheng Y, Luo H, Izzo F, Peng H, Wang Z, Yu T, Zhang Y, et al. ALKBH5–N6-Methyladenosine by IGF2BP proteins enhances mRNA stability and translational efficiency. Cell 2020;182:2381–2395.e10.

26. Weng H, Huang H, Wu H, Qin X, Zhao BS, Dong L, et al. METTL14 inhibits pro-metastatic HSP90-mediated monocytic macrophage polarization and promotes tumor growth in ovarian cancer. Oncogene. 2019;38:2747–2757.

27. Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, et al. N6-methyladenosine in nuclear RNA demethylase that impacts RNA metabolism and mouse fertility. Mol Cell. 2013;49:18–29.

28. Peng W, Li J, Chen R, Gu Q, Yang P, Qian W, et al. Upregulated METTL3 promotes metastasis of colorectal Cancer via miR-1246/SPRED2/MAPK signaling pathway. J Exp Clin Cancer Res. 2019;38:393.

29. Wang H, Deng Q, Lu Z, Ling Y, Hou X, Chen Z, et al. N6-methyladenosine induced miR-143-3p promotes the brain metastasis of lung cancer via regulation of VASH1. Mol Cancer. 2019;18:181.

30. Morfert A, Di Minin G, Postmayr A, Freimann R, Areti F, Thore S, et al. Identification of Spen as a Crucial Factor for Xist Function through Forward Genetic Screening in Hayplod Embryonic Stem Cells. Cell Rep. 2015;12:1554–61.

31. Path DP, Chen CK, Pickering BF, Chow A, Jackson C, Gutmann M, et al. m6A RNA methylation promotes XIST-mediated transcriptional repression. Nature. 2016;535:369–73.

32. Nesterova TB, Wei G, Coker H, Pintacuda G, Bowness J, Zhang T, et al. Systematic allelic analysis defines the interplay of key pathways in X chromosome inactivation. Nat Commun. 2019;10:3129.

33. Liu J, Zhang X, Chen K, Cheng Y, Liu S, Xia J, et al. CCRC Chemokine Receptor-Inducible Inc-Dmp3 Restrains Dendritic Cell Migration by Inhibiting Hifo-Mediated Glycolysis. Immunity. 2019;50:600–615.e15.

34. Liu P, Zhang B, Chen Z, He Y, Du Y, Liu Y, et al. m6A-induced IncRNA MALAT1 aggravates renal fibrogenesis in obstructive nephropathy through the miR-145/FAK pathway. Aging. 2020;12:25280–99.

35. Zhang S, Zhao BS, Zhou A, Lin K, Zheng S, Lu Z, et al. m6A Demethylase ALKBHS Maintains Tumorigenicity of Glioblastoma Stem-like Cells by Sustaining FOXL1 expression and Cell Proliferation Program. Cancer Cell. 2017;31:591–606.e6.

36. Zhang K-I, Tan XL, Guo L. The long non-coding RNA DANC2 regulates the inflammatory phenotype of breast cancer cells and promotes breast cancer progression via EZH2-dependent suppression of SOCS3 transcription. Mol Oncol. 2020;14:309–28.

37. Lin Y, Yang F, Qi X, Li Q, Wang D, Yi T, et al. LncRNA DANC2 promotes tumor growth and angiogenesis in ovarian cancer through direct targeting of miR-145. Mol Cancer. 2019;18:2286–96.

38. Hu X, Peng W-X, Zhou H, Jiang J, Zhou X, Huang D, et al. IGF2B2 regulates macrophage polarization and promotes therapeutic adipose tissue remodeling. Mol Metab. 2018;20:285–95.

39. Ji P, Diederichs S, Wang W, Boing S, Metzger R, Schneider PM, et al. MALAT1: a druggable long non-coding RNA for targeted anti-cancer approaches. J Hematol Oncol. 2018;11:63.

40. Brown JA, Bulkley D, Wang J, Valenstein ML, Yario TA, Steitz TA, et al. M6A-mediated repression of mRNAs in male germ cells. Proc Natl Acad Sci U S A. 2015;112:7680–5.

41. Gu S, Sun D, Dai H, Zhang Z. N6-methyladenosine mediates the cellular adaptive response to HIF-1α-mediated Glycolysis. Immunity. 2019;50:600–615.e15.

42. Amodio N, Raimondi L, Juli G, Stamato MA, Caracciolo D, Tagliaferri P, et al. Genetic Screening in Haploid Embryonic Stem Cells. Cell Rep. 2015;12:554–61.

43. Yang P, Li J, Chen R, Ye H, Hu C, Wang C, et al. Excessive miR-25-3p maturation via N6-methyladenosine stimulation by cigarette smoke promotes pancreatic cancer progression. Nat Commun. 2019;10:1858.

44. Han J, Wang J-Z, Yang X, Yu H, Zhou R, Lu H-C, et al. METTL3 promotes tumor proliferation of bladder cancer by accelerating pri-miR221/222 maturation in m6A-dependent manner. Mol Cancer. 2019;18:1110.
complex with HSPA1A and YBX1 in head and neck squamous cell carcinoma. Mol Oncol. 2020;14:128-96.

67. Zheng Z-Q, Li Z-X, Zhou G-Q, Lin L, Zhang L-L, Lv J-W, et al. Long Noncoding RNA FAM225A Promotes Nasopharyngeal Carcinoma Tumorigenesis and Metastasis by Acting as a Cellfree mRNA to Sponge miR-590-3p/miR-1275 and Upregulate TGFβ3. Cancer Res. 2019;79:4612–26.

68. Wu Y, Yang X, Chen Z, Tian L, Jiang G, Chen F, et al. m6A-induced IncRNA RP11 triggers the dissemination of colorectal cancer cells via upregulation of Zeb1. Mol Cancer. 2019;18:87.

69. Jin D, Guo J, Wu Y, Du J, Yang L, Wang X, et al. m6A mRNA methylation initiation by METTL3 directly promotes YAP translation and increases YAP activity by regulating the MALAT1-miR-1914-3p-YAP axis to induce NSCLC drug resistance and metastasis. J Hematol Oncol. 2019;12:35.

70. Yang X, Zhang S, He C, Xue P, Zhang L, He Z, et al. METTL14 suppresses proliferation and metastasis of colorectal cancer by down-regulating oncogenic long non-coding RNA XIST. Mol Cancer. 2020;19:496.

71. Zhao J, Lee EE, Kim J, Yang R, Chamseddin B, Ni C, et al. Transforming growth factor-β (TGF-β) modulates N6-methyladenosine Levels by Targeting the 3′–5′-Exonuclease. Eur Rev Med Pharmacol Sci. 2018;22:8220–42.

72. Wang S, Zhang Y, Cai Q, Ma M, Jin LY, Weng M, et al. Circular RNA FOXP1 facilitates gastric cancer growth and invasion via NURF complex-dependent activation of transcription factor SOX4. Mol Cancer. 2019;18:45.

73. Li X, Yang L, Chen L-L. The Biogenesis, Functions, and Challenges of Circular RNAs. Mol Cell. 2018;71:428–42.

74. Di Tintoreto G, Dattilo G, Centrone-Broca A, Colantoni A, Guarnacci M, Rossi F, et al. Modulation of circRNA Metabolism by m6A Modification. Cell Rep. 2020;33:107641.

75. Pamudurti NR, Barot K, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, et al. Translation of CircRNAs. Mol Cell. 2017;66:21–e7.

76. Legnini I, Di Tintoreto G, Rossi F, Morlando M, Briganti F, Shanderi O, et al. Circ-ZNF609 Is a Circular RNA that Can Be Translated and Functions in Myogenesis. Mol Cell. 2017;66:22–37.

77. Zhou C, Mollinan B, Daneshvar K, Pondick JV, Wang J, Van Wittenberghe N, et al. Genome-Wide Maps of mi6a circRNAs Identify Widespread and Cell-Type-Specific Methylation Patterns that Are Distinct from miRNAs. Cell Rep. 2017;20:2252–66.

78. Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, et al. Extensive translation of circular RNAs driven by N6-methyladenosine. Cell Res. 2017;27:626–38.

79. Chen YG, Chen R, Ahmad S, Verma R, Kasturi SP, Amaya L, et al. N6-Methyladenosine Modification Controls Circular RNA Immunity. Mol Cell. 2019;76:96–109.

80. Du WW, Yang W, Li X, Awan FM, Zhang Z, Fang L, et al. Circular RNA circ-DNMT1 enhances breast cancer progression by activating autophagy. Oncogene. 2018;37:3892–94.

81. Ding L, Zhao Y, Dang S, Wang Y, Li X, Yu X, et al. Circular RNA circ-DONSON facilitates gastric cancer growth and invasion via NURF complex dependent activation of transcription factor SOX4. Mol Cancer. 2019;18:45.

82. Wang S, Zhang Y, Cai G, Ma M, Jin LY, Weng M, et al. Circular RNA FOXP1 promotes tumor progression and Warburg effect in gallbladder cancer by regulating PKLR expression. Mol Cancer. 2019;18:143.

83. Wang S, Zhang Y, Huang Y, Wang L, Zhu K, et al. m6A demethylase ALKBH5 promotes tumor progression and Warburg effect in gallbladder cancer. Cell Stem Cell. 2015;16:289–91.

84. Zhao J, Lee EE, Kim J, Yang R, Chamseddin B, Ni C, et al. Transforming growth factor-β (TGF-β) modulates N6-methyladenosine Levels by Targeting the 3′–5′-Exonuclease. Eur Rev Med Pharmacol Sci. 2018;22:8220–6.

85. Sun H-D, Xu Z-P, Sun Z-Q, Zhu B, Wang Q, Zhou J, et al. MiR-33a suppresses proliferation of NSCLC cells via targeting METTL3 mRNA. Biochem Biophys Res Commun. 2017;482:562–9.

86. Wang S, Zhang Y, Cai Q, Ma M, Jin LY, Weng M, et al. Circular RNA FOXP1 promotes tumor progression and Warburg effect in gallbladder cancer. Cell Stem Cell. 2015;16:289–91.

87. Li Y, Yang F, Gao M, Gong R, Jin M, Liu T, et al. miR-149-3p Regulates the Switch between Adipogenic and Osteogenic Differentiation of BMSCs by Targeting FTO. Mol Ther Nucleic Acids. 2019;17:590–600.

88. Shen X-P, Ling X, Lu H, Zhou C-X, Zhang J-K, Yu Q. Low expression of microRNA-1266 promotes colorectal cancer progression via targeting FTO. Eur Rev Med Pharmacol Sci. 2018;22:8220–6.

89. Yang Z, Li J, Feng G, Sao W, Yang Y, Zhang S, et al. MicroRNA-145 Modulates N6-Methyladenosine Levels by Targeting the 3′-Untranslated mRNA Region of the N6-Methyladenosine Binding YTH Domain Family 2 Protein. J Biol Chem. 2017;292:3614–23.

90. Du M, Zhang Y, Mao Y, Mou J, Zhao J, Xue Q, et al. MiR-33a suppresses proliferation of NSCLC cells via targeting METTL3 mRNA. Biochem Biophys Res Commun. 2017;482:562–9.

91. Fang C, Chen Y-X, Wu N-Y, Yin J-Y, Li X-P, Huang H-S, et al. METTL14 suppresses proliferation and cisplatin sensitivity in non-small-cell lung cancer (NSCLC) cells by activating the eIF3a-mediated NER signaling pathway. Sci Rep. 2017;7:40384.

92. Wei W, Hsu B, Shi X. m6R-RIP inhibits lung cancer via downregulating the expression of METTL3. Cancer Manag Res. 2019;11:1177–87.

93. Xu X, Yu Y, Zong K, Gu P, Tu Y. Up-regulation of IGFBP2 by multiple mechanisms in pancreatic cancer promotes cancer proliferation by activating the PI3K/Akt signaling pathway. J Exp Clin Cancer Res. 2019;38:497.
111. Zhu L, Zhu Y, Han S, Chen M, Song P, Dai D, et al. Impaired autophagic degradation of lncRNA ARHGAP5-AS1 promotes chemoresistance in gastric cancer. Cell Death Dis. 2019;10:383.

112. Klinge CM, Piell KM, Tookey CS, Rouchka EC. HNRNPA2/B1 is upregulated in endocrine-resistant LCC9 breast cancer cells and alters the miRNA transcriptome when overexpressed in MCF-7 cells. Sci Rep. 2019;9:9430.

113. Li Z, Weng H, Su R, Weng X, Zuo Z, Li C, et al. FTO Plays an Oncogenic Role in Acute Myeloid Leukemia as a N6-Methyladenosine RNA Demethylase. Cancer Cell. 2017;31:127–41.

114. Paris J, Morgan M, Campos J, Spencer GJ, Shmakova A, Ivanova I, et al. Targeting the RNA m6A Reader YTHDF2 Selectively Compromises Cancer Stem Cells in Acute Myeloid Leukemia. Cell Stem Cell. 2019;25:137–148.e6.

115. Huang Y, Su R, Sheng Y, Dong L, Dong Z, Xu H, et al. Small Molecule Targeting of Oncogenic FTO Demethylase in Acute Myeloid Leukemia. Cancer Cell. 2019;35:677–691.e10.

116. Zhang B, Wu Q, Li B, Wang D, Wang L, Zhou YL. m6A regulator-mediated methylation modification patterns and tumor microenvironment infiltration characterization in gastric cancer. Mol Cancer. 2020;19:53.

117. Hou J, Zhang H, Liu J, Zhao Z, Wang L, Lu Z, et al. YTHD2 reduction fuels inflammation and vascular abnormalization in hepatocellular carcinoma. Mol Cancer. 2019;18:163.

118. Zhu S, Wang J-Z, Chen D, He Y-T, Meng N, Chen M, et al. An oncopeptide regulates m6A recognition by the m6A reader IGF2BP1 and tumorigenesis. Nat Commun. 2020;11:1685.

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