Genes & Diseases (2024) 11, 101045

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REVIEW ARTICLE

The landscape of epigenetic regulation and therapeutic application of N^6-methyladenosine modifications in non-coding RNAs

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Received 17 November 2022; received in revised form 18 May 2023; accepted 4 June 2023
Available online 18 July 2023

KEYWORDS
Circular RNA;
Epigenetic regulation;
Long non-coding RNA;
MicroRNA;
Non-coding RNA;
RNA m^6A modification

Abstract RNA N^6-methyladenosine (m^6A) methylation is the most abundant and conserved RNA modification in eukaryotes. It participates in the regulation of RNA metabolism and various pathophysiological processes. Non-coding RNAs (ncRNAs) are defined as small or long transcripts which do not encode proteins and display numerous biological regulatory functions. Similar to mRNAs, m^6A deposition is observed in ncRNAs. Studying RNA m^6A modifications on ncRNAs is of great importance specifically to deepen our understanding of their biological roles and clinical implications. In this review, we summarized the recent research findings regarding the mutual regulation between RNA m^6A modification and ncRNAs (with a specific focus on microRNAs, long non-coding RNAs, and circular RNAs) and their functions. We also discussed the

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Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2023.06.015

challenges of m^{6}A-containing ncRNAs and RNA m^{6}A as therapeutic targets in human diseases and their future perspective in translational roles.

Introduction

Epigenetic regulation is critical to many fundamental cellular processes and contributes towards the diversity of physiopathology functions.[1–3] In the last few decades, histone and DNA modifications have been extensively investigated, and many excellent breakthroughs have been made from bench to clinical application.[4,5] Recently, RNA modifications have gained widespread interest. An ever-increasing number of studies have identified a number of RNA modifications in the eukaryotic transcriptome, including 5-methylcytosine (m^{5}C), pseudouridine (Ψ), N^1-methyladenosine (m^{1}A), and N^6-methyladenosine (m^{6}A) methylation.[6] Among them, the RNA m^{6}A methylation is most abundant in eukaryotes and has been observed to be consistently conserved in mammals. RNA m^{6}A modification participates in the modulation of RNA metabolism and various pathophysiological processes, such as translation, RNA splicing, and degradation.[7] Dysregulation of RNA m^{6}A methylation is closely related to the occurrence and development of various diseases including tumorigenesis, Alzheimer's disease, and cardiovascular diseases.[8–10]

Non-coding RNAs (ncRNAs) are RNA molecules that are not translated into proteins. Contrary to earlier views, they have been identified to have myriad biological roles and are emerging as master regulators of cellular processes.[11] Various types of ncRNAs have been reported, such as microRNAs (miRNAs), ribosomal RNAs (rRNAs), long non-coding RNAs (lncRNAs), small nuclear RNAs (snRNAs), and circular RNAs (circRNAs). With the development of more practical methods for examining RNA m^{6}A modifications, insights into the underlying mechanisms have been uncovered in recent years.[12–14] The m^{6}A modification can be used to modify all the different types of RNAs. Although great progress has been made in the scientific approach involved in understanding the regulatory mechanism of RNA m^{6}A modification in mRNAs, the deposition of m^{6}A modifications in ncRNAs and its underlying regulatory roles are still in its infancy. In this review, we will discuss the research advances in the realm of RNA m^{6}A modification and its function in ncRNAs primarily on miRNAs, lncRNAs, and circRNAs, and address the potential therapeutic strategies to target RNA m^{6}A regulators for disease therapy, as well as outline some outstanding questions and challenges that require further exploration in this field.

Regulation of RNA m^{6}A modification

The RNA m^{6}A modification was first discovered in mRNA fractions obtained from Novikoff-hepatoma cells.[15,16] Like DNA methylation, RNA m^{6}A methylation also has a reversible and dynamic post-transcriptional modification in mammalian.[17] Both efficacy and abundance of m^{6}A modification on RNA are regulated under the dynamic interaction among methyltransferases ("writers"), demethylases ("erasers"), and binding proteins ("readers") (Fig. 1)[7].

Methyltransferases are generally referred to as "writers". They consist of nuclear methyltransferases made up of methyltransferase-like 13 (METTL3), METTL14, and WTAP, which append the m^{6}A modification and thereby significantly influence certain physio-pathological processes.[18] METTL3 and METTL14 contain a methyltransferase domain (MTD) that can catalyze the transfer of a methyl group from S-adenosylmethionine to the N^6 of adenosine (A). The crystal structure of the METTL3-METTL14 heterodimer reveals that METTL3 and METTL14 are tightly bound to each other.[19] WTAP has been functionally linked to its role in alternative splicing and mediates METTL3/14 complex localized to the nuclear speckles.[20–22] In addition, the METTL3/METTL14/WTAP complex recruits other cofactors, such as RBM15, METTL16, and RBM15B (which directs the adenosine methylation in mRNAs and lncRNAs), KIAA1429, and ZC3H13 to mediate the methylation of methyltransferases to RNAs.[23–25]

Demethylases, also named "erasers", include α-ketoglutarate-dependent dioxygenase alkB homolog 5 (ALKBH5), and fat mass and obesity-associated protein (FTO), that catalyze RNA m^{6}A demethylation.[7,26,27] Both ALKBH5 and FTO belong to the Fe (II)/α-ketoglutarate dependent dioxygenase enzyme family. FTO was the first identified RNA m^{6}A demethylase in mammal cells,[27] and ALKBH5 was the second one to be discovered. Unlike FTO, which can demethylate both DNA and RNA m^{6}A methylations, ALKBH5 only specifically demethylated m^{6}A-modifications of RNA.[28] Besides, another alkB family protein ALKBH3 was also found to demethylate m^{6}A modifications in tRNA.[29] However, another contrasting study suggested that ALKBH3 could specifically demethylate only m^{1}A and m^{3}C in tRNA, but demonstrated no demethylase activity on m^{6}A modifications.[30] Therefore, if ALKBH3 has demethylase activity on tRNA m^{6}A modification remains conflicting and requires further investigation.

The entire process of RNA m^{6}A modifications seems to be limited to methylation and demethylation. However, these chemical modifications could have a direct effect on RNA transcription by affecting several properties such as RNA secondary structure, charge, protein-RNA interactions, and base-pairing, which in turn modulate gene expression by regulating RNA processing, localization, translation, and degradation.[31] RNA m^{6}A binding proteins, including heterogeneous nuclear ribonucleoprotein (HNRNP) proteins, YT521-B homology (YTH) domain family, and insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family, are termed

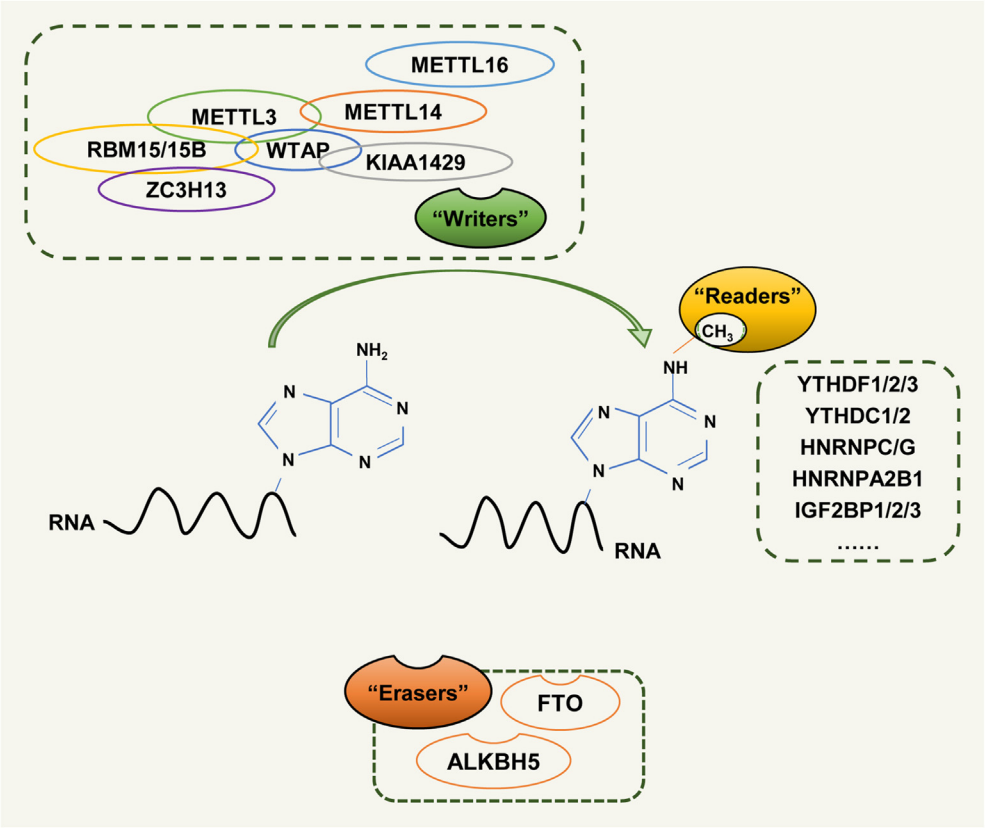

Figure 1 The dynamic and reversible RNA m^{6}A modification process. m^{6}A modifications on RNAs are regulated by the dynamic interaction between methyltransferases ("writers"), demethylases ("erasers"), and binding proteins ("readers").

as "readers" that can specifically recognize m^{6}A sites, which shows that m^{6}A modification could affect RNA processing by recruiting specific proteins.[7,32–34] The YTH protein family is composed of a series of proteins such as YTHDF1-3 and YTHDC1-2 that recognize m^{6}A-modified transcripts. YTHDF1 selectively binds to m^{6}A-methylated mRNA and increases mRNA translation efficiency.[35] On the contrary, YTHDF2 selectively binds to m^{6}A modification that regulates RNA degradation.[36,37] Alternatively, YTHDF3 binds to m^{6}A-modified transcripts along with either YTHDF1 or YTHDF2, indicating the close association among YTHDF1-3 proteins to regulate the turnover (translation and decay) of mRNA targets.[38] Unlike YTHDFs located in the cytosol, YTHDC1 and YTHDC2 are nuclear proteins. YTHDC1 regulates m^{6}A methylated RNA splicing and nuclear export.[39,40] YTHDC2 contains a DEAH RNA helicase domain as well as a YTH m^{6}A binding domain. Hence, the role of YTHDC2 in cells is much more complicated and remains uncertain. It has been reported that YTHDC2 could modulate the translation efficiency of the m^{6}A-containing target mRNA and decrease its abundance.[41] The IGF2BP proteins also recognize the m^{6}A-modified mRNA, but in contrast with the YTH family proteins, enhance the mRNA stability and translation.[33,42,43] With respect to HNRNP "readers", the m^{6}A RNA modification alters the local structure of RNA, thereby, increasing the accessibility of target RNA to bind with HNRNP proteins.[44,45] Moreover, HNRNPA2B1 also participates in primary miRNA processing and alternative splicing.[34]

Mutual regulation between RNA m^{6}A modification and miRNAs

MicroRNAs (miRNAs) are a group of non-coding single-stranded RNAs with a length of about 22 nucleotides, involved in the modulation of post-transcriptional gene expression.[46–49] The biogenesis of miRNA is primarily produced by the transcriptional activity of RNA polymerase II or III to form the primary miRNAs (pri-miRNAs). Then the pri-miRNAs are processed by endonuclease Drosha and double-stranded RNA binding protein DGCR8 to generate precursor miRNAs (pre-miRNAs). Finally, the pre-miRNAs are transported to the cytoplasm by RanGTP and exportin-5 to form mature miRNAs, spliced by the endoribonuclease Dicer. RNA m^{6}A modifications have been found to take part in the regulation of pri-miRNA processing and pre-miRNA splicing (Fig. 2).

RNA m^{6}A methyltransferases have been reported to methylate pri-miRNAs, and consequently increase the binding and processing of pri-miRNAs by DGCR8 and increase the splicing by Dicer to pre-miRNAs.[50,51] The RNA-binding protein HNRNPA2B1 has been shown to recognize the m^{6}A-containing pri-miRNAs and affect pri-miRNAs processing.[34] Altered m^{6}A RNA modification of pri-miRNAs or pre-miRNAs not only induces the change in the expression levels of many mature miRNAs but also takes critical roles in various diseases.[50,52] METTL3-mediated m^{6}A methylation

of pre-miR-320 has been found to promote osteogenic differentiation of bone marrow-derived mesenchymal stem cells.[53] During the progression of pancreatic cancer, hypomethylation of the METTL3 promoter was observed to increase its expression, significantly elevating the m^{6}A deposition of pri-miR-25 to promote the generation of mature miR-25, and consequently, aggravating the development and progression of pancreatic cancer.[54] Similarly, METTL3 was seen to promote bladder cancer via accelerating pri-miR-221/222 maturation in an RNA m^{6}A-dependent manner.[52] Another study also reported that METTL3 up-regulation could contribute to the abnormal m^{6}A modification in colorectal cancer and exacerbate tumor metastasis via the methylation of pri-miR-1246.[55] On the contrary, forced expression of METTL3 was noted to alleviate colistin-induced renal injury by modulating the miR-873−5p maturation process through DGCR8 in an m^{6}A-dependent manner.[56] Unlike METTL3, METTL14-mediated m^{6}A methylation of pri-miR-375 processing was able to up-regulate the expression and the maturation of miR-375, and thereby, inhibit colorectal cancer cell growth and metastasis.[57] Moreover, METTL14/m^{6}A was also reported to suppress tumor invasion and metastasis by regulating the processing of miR-126 by DGCR8 in hepatocellular carcinoma.[58]

RNA m^{6}A demethylases also contribute to the methylation status of miRNAs. Contrary to the well-characterized role of methyltransferase in the context of miRNA-processing, the specific function of demethylases is not quite thoroughly studied. Demethylase ALKBH5 has been found to interact with DEAD-box RNA helicase DDX3 and recruited AGO2 protein to modulate the expression of methylated-

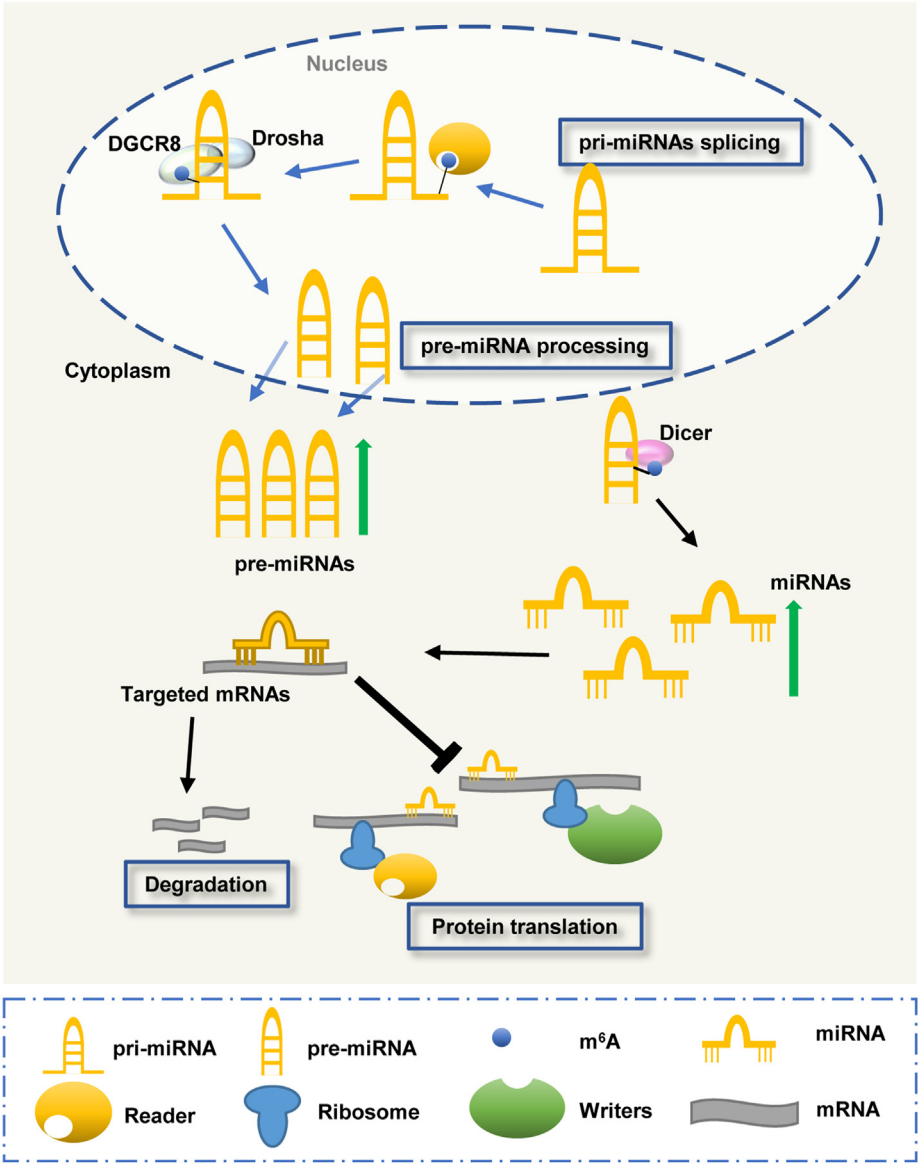

Figure 2 The regulation of RNA m^{6}A methylation on miRNAs. RNA m^{6}A methylation participates in the regulation of pri-miRNAs processing and pre-miRNA splicing to modulate the expression of mature miRNAs, and consequently, to regulate miRNA and target mRNA interaction.

miRNAs.[59] Besides, ALKBH5 was also observed to negatively regulate miR-7 expression through physical interaction with HuR to suppress the process of miR-7 during epithelial ovarian cancer progression.[60] Interestingly, the knockdown of another RNA m^{6}A demethylase FTO was able to reduce miRNA expression without affecting the primary transcripts of many miRNAs.[61] FTO knockdown in cardiomyocytes could increase miR-133a expression via the m^{6}A binding protein IGF2BP2.[62] Thus, further investigations to illustrate the underlying regulatory mechanisms of demethylases would have a tremendous impact on understanding their role in miRNA biogenesis.

In addition to the regulation of miRNAs by RNA m^{6}A modification, the 3′- untranslated RNA region (UTR) of effector mRNAs can also be targeted by mature miRNAs to facilitate the degradation of targeted mRNAs and inhibit protein translation. miR-145 regulated RNA m^{6}A modification via targeting the 3′-UTR of m^{6}A modification reader protein YTHDF2.[63] Also, miR-4429 has been found to prevent gastric cancer progression by regulating its target gene METTL3.[64] Moreover, YTHDF1 was also identified to contribute to the glioma progression, through the role of miR-3436 that bound to the 3′-UTR of YTHDF1 upstream to regulate YTHDF1 expression in glioma.[65] Taken together, the miRNA-m^{6}A methylation can regulate each other in both ways. On one hand, RNA m^{6}A methylation participates in the regulation of pri-miRNAs processing and pre-miRNA splicing to modulate mature miRNA expression. On the other hand, miRNAs could act as the upstream factor of RNA m^{6}A methylation regulator proteins by targeting their mRNAs (Table 1).

Mutual regulation between RNA m^{6}A modification and lncRNAs

Accumulating evidence indicates that lncRNAs take critical roles in various biological functions and the pathophysiology of many diseases. Like messenger RNAs (mRNAs), lncRNAs are transcribed by RNA polymerase II and undergo splicing, capping, and polyadenylation.[66,67] Since the discovery of lncRNAs, numerous underlying mechanisms involved in their post-transcriptional regulation have been unraveled. Based on recent research on the distribution of m^{6}A in the transcriptome, lncRNAs with m^{6}A modification have been identified and reported to take part in the physiology and pathology of human diseases.[68–70]

In recent years, an increasing number of studies have reported m^{6}A modifications on lncRNAs and have expanded our knowledge about the regulatory mechanisms of lncRNA as well as their m^{6}A methylation (Fig. 3). One of the proposed mechanisms is called the "m^{6}A-switch" wherein the RNA m^{6}A modification would alter the local structure of lncRNA and control RNA-protein interactions for biological regulation.[44,45] m^{6}A-methylated hairpin formation of the lncRNA metastasis-associated lung adenocarcinoma

Table 1 Mutual regulation between RNA m^{6}A modification and miRNAs.

miRNAs	RNA m^{6}A effectors	Mechanism	Biological function	References
The effect of RNA m^{6}A methylation on miRNA				
miR-320	METTL3	METTL3 mediated m^{6}A methylation on pre-miR-320	Promotes osteogenic differentiation	53
miR-25	METTL3	METTL3 increased the m^{6}A deposition in pri-miR-25	Promotes progression of pancreatic cancer	54
miR-221/222	METTL3	METTL3 elevated the m^{6}A deposition in pri-miR-221/222	Promotes bladder cancer	52
miR-1246	METTL3	METTL3 increased the m^{6}A deposition in pri-miR-1246	Promotes colorectal cancer and tumor metastasis	55
miR-873—5p	METTL3	METTL3 modulated miR-873—5p mature process through DGCR8	Alleviates colistin-induced renal injury	56
miR-375	METTL14	METTL14 mediated m^{6}A methylation on pri-miR-375 processing	Inhibits colorectal cancer cell growth and metastasis	57
miR-126	METTL14	METTL14/m^{6}A regulated miR-126 processing by DGCR8	Inhibits hepatocellular carcinoma	58
miR-7	ALKBH5	ALKBH5 suppressed miR-7 processing	Promotes epithelial ovarian cancer	60
miR-133a	FTO	FTO knockdown increased miR-133a expression via m^{6}A binding protein IGF2BP2	Prevents cardiac proliferation and promotes cardiac pathological hypertrophy	62
The effect of miRNA on RNA m6A methylation				
miR-145	YTHDF2	3′-UTR of YTHDF2 targeted by miR-145	YTHDF2 correlated with increased malignancy of hepatocellular carcinoma.	63
miR-4429	METTL3	3′-UTR of METTL3 targeted by miR-4429	Prevents gastric cancer progression	64
miR-3436	YTHDF1	3′-UTR of YTHDF1 targeted by miR-3436	High expression of YTHDF1 in glioma was associated with worse overall survival	65

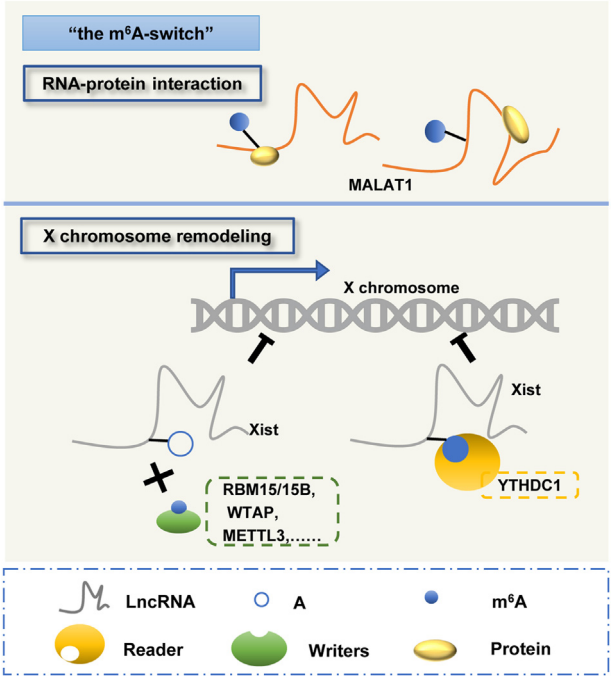

Figure 3 The regulation of lncRNAs by RNA m^{6}A modification. RNA m^{6}A modification of lncRNAs has an impact on RNA-protein interaction (*e.g.*, MALAT1) and chromatin remodeling (*e.g.*, Xist).

transcript 1 (MALAT1), one of the well-characterized lncRNAs, resulted in a much stronger binding of MALAT1 with heterogeneous nuclear ribonucleoprotein C and heterogeneous nuclear ribonucleoprotein *G*, thus affecting nucleus gene expression and maturation[68,44,.45] Akin to MALAT1, X-inactive specific transcript (Xist) is highly methylated with many m^{6}A modification sites.[23] Several proteins which are the components of the m^{6}A methylation complex and the m^{6}A binding proteins, including RBM15/15B, WTAP, METTL3, and YTHDC1, have been identified to bind Xist and are in fact required for Xist-mediated transcriptional silencing of genes on the *X* chromosome.[23,71,72]

The regulation between m^{6}A modification and lncRNAs also contributes to critical pathological roles in several diseases (Fig. 4). In glioma, METTL3 promoted the malignant progression of gliomas through up-regulation of m^{6}A methylated-MALAT1 stability.[73] Several investigations have focused on discovering the mechanism for the oncogenic role of m^{6}A methylated-MALAT1; using mutations and super-resolution imaging, the m^{6}A modification on MALAT1 was demonstrated to be recognized by YTHDC1 which taken an essential role in regulating the metastatic potential of cancer cells.[74] One study revealed that MALAT1 bound to METTL14 mediated the interaction between fusion protein PML-RARα, and aggravated the leukemia progression by modulating chimeric mRNA export via YTHDC1 recognition.[75] Similarly, METTL14-mediated RNA m^{6}A modification regulated Xist expression in colorectal cancer and contributed towards tumor growth and invasion.[76] Interestingly, another study found that Xist-mediated gene silencing is mostly attributed to synergistic actions of Spen/A-repeat and Polycomb/B-repeat, on comparison with LBR and Rbm15/m^{6}A-methyltransferase complex that contributes minorly in mouse embryonic stem cell-based models.[77] These studies appear to be inconsistent indicating that the role of m^{6}A modification on lncRNAs might be selectively regulated or show distinct regulatory function under specific stimulants in a cell type-specific manner. Further studies focusing on the specific pathological role of m^{6}A-methylated RNA during different diseases are essential as this would be an opportunity to better clarify the association between m^{6}A RNA modifications and lncRNAs under specific conditions.

In addition to MALAT1 and Xist, other m^{6}A-methylated lncRNAs have also been identified. Colorectal cancer-associated lncRNA RP11 can be positively regulated by RNA m^{6}A modification and enhance cancer cell metastasis.[78] m^{6}A-methylated lncRNA NEAT1 facilitated oncogenic complex, and NEAT1 with a high m^{6}A level corelated with the bone metastasis of prostate cancer.[79] Another lncRNA, FAM225A, which was an oncogenic m^{6}A-methylated lncRNA in nasopharyngeal carcinogenesis, has been found to act as the competing endogenous RNA for miR-590—3p and miR-1275 to promote carcinoma development and progression.[80] In gastric cancer, lncRNA THAP7-AS1 was up-regulated and facilitated CUL4B entry into the nucleus to promote gastric cancer cell growth, invasion, and metastasis.[81] A further in-depth study revealed that METTL3-mediated m^{6}A methylation stabilized THAP7-AS1 by m^{6}A binding to protein IGF2BP1.[81] METTL3 also increased m^{6}A-modified lncRNA SNHG17 to promote gefitinib resistance in lung adenocarcinoma.[82] RNA m^{6}A-modified lncRNA LINREP up-regulation promoted glioblastoma multiforme progression and its up-regulation was related to poor prognosis in glioma patients.[83] Mechanistically, METTL3 suppression decreased the m^{6}A methylation level and RNA expression level of LINREP, and the stability of LINREP was enhanced by HuR in an m^{6}A-dependent manner.[83] Similarly, m^{6}A methylation in RMRP and DIAPH1-AS1 also enhanced its stability, and RMRP or DIAPH1-AS1 elevation facilitated cancer progression.[84,85] In addition to regulating expression, lncRNA splicing was also found to be regulated by RNA m^{6}A methylation. In gemcitabine resistance pancreatic cancer cells, the m^{6}A modification level of lncRNA ANRIL was significantly increased, and METTL3-mediated m^{6}A methylation elevation played a pivotal role in the occurrence of SRSF3-mediated ANRIL splicing events.[86] Except for oncogenic lncRNAs, lncRNAs with m^{6}A modification have also been found to inhibit the progression of cancers. METTL16 directly bound m^{6}A-methylated lncRNA RAB11B-AS1 and decreased its stability, RAB11B-AS1 down-regulation led to poor prognosis in patients with hepatocellular carcinoma.[87] LncRNA ZNRD1-AS1 was inhibited by m^{6}A binding protein YTHDC2, and overexpression of ZNRD1-AS1 suppressed the progression of lung cancer.[88] LncRNA GAS5 was negatively regulated by the m^{6}A reader YTHDF3 and suppressed the progression of colorectal cancer.[89] WTAP-mediated m^{6}A methylation on lncRNA NORAD can promote nucleus pulposus cells' senescence and intervertebral disc degeneration development.[90] Mechanically, the stability of lncRNA NORAD was regulated by YTHDF2 in an RNA m^{6}A-dependent manner, and histone modification H3K4me3-induced WTAP would increase NORAD's m^{6}A methylation level and promote its degradation.[90] In addition, knockdown of m^{6}A-

modified mmu-lncRNA 121686/hsa-lncRNA 520657 can attenuate acute kidney injury.[91] RNA m^{6}A reader YTHDC1 can decrease m^{6}A-modified lncRNA FENDRR's stability to enhance pyroptosis in hypoxic pulmonary artery endothelial cells.[92] Moreover, similar to miRNAs, lncRNAs could also be found to regulate the expression of RNA m^{6}A effectors to affect cellular m^{6}A methylation and recognition. LncRNA DNA methylation-deregulated and RNA m^{6}A reader-cooperating lncRNA (DMDRMR) enhances the activity of IGF2BP3 thereby regulating its target genes in an m^{6}A-dependent manner.[93] MALAT1 increased IGF2BP2 expression in thyroid cancer and promoted its target gene MYC expression through m^{6}A recognition.[94] Considering all the recent research in m^{6}A regulation of lncRNAs, like the variety of lncRNA functions and mechanisms, the m^{6}A RNA modifications on lncRNAs have a very complex and changeable regulatory mechanism. Towards understanding this, further studies are certainly necessary to explore the role of m^{6}A-methylated lncRNAs that could provide new insights with respect to diseases diagnosis, treatment, and prognosis, as well as expand our fundamental understanding of the "RNA metabolism" world (Table 2).

Mutual regulation between RNA m^{6}A modification and circular RNAs

Apart from traditional ncRNAs, circular RNAs (circRNAs) are emerging as a novel class of endogenous ncRNAs that form covalently closed circle structures. CircRNAs are widely distributed throughout the body, across different types of tissues and organs, and participate in diverse biological and pathophysiological processes.[95–97] CircRNAs have been found to function as miRNA decoys and bind to RNA-binding proteins.[95] Some circRNAs can be translated into proteins or peptides to exert their regulatory roles.[98] Like mRNAs and other ncRNAs, mutual regulation between RNA m^{6}A and circRNAs also contributes to circRNAs' biology and function.[99,100]

A recent study on genome-wide profiling revealed that RNA m^{6}A modifications were widespread in circRNAs, and exhibited distinct m^{6}A patterns compared with mRNAs.[101] CircRNAs can also be translated into proteins in a cap-independent translation mechanism through an internal ribosomal entry site or RNA m^{6}A modification.[98,102] Therefore, the translation efficiency of m^{6}A-methylated

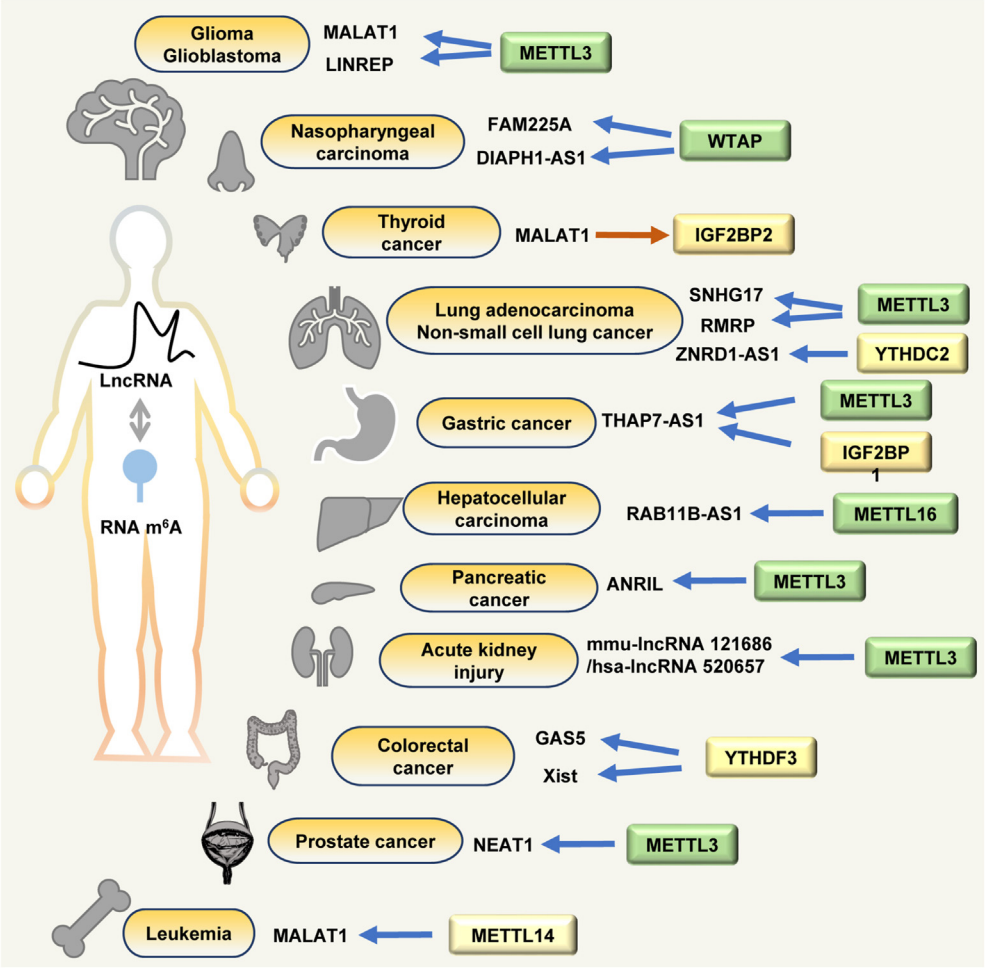

Figure 4 Mutual regulation between RNA m^{6}A and lncRNAs in human diseases. RNA m^{6}A regulates m^{6}A-methylated-lncRNAs and some lncRNAs are also found to regulate the expression of RNA m^{6}A effectors to affect cellular m^{6}A methylation and recognition in several human diseases.

Table 2 Mutual regulation between RNA m^{6}A modification and lncRNAs.

LncRNAs	RNA m^{6}A effectors	Mechanism	Biological function	References
The effect of RNA m^{6}A methylation on lncRNA				
MALAT1	METTL3	METTL3 up-regulates m^{6}A-methylated MALAT1 stability	Promotes the progression of gliomas	73
MALAT1	YTHDC1	M^{6}A-methylated MALAT1 recruits YTHDC1 to nuclear speckles	Promotes cancer metastasis	74
MALAT1	YTHDC1	MALAT1 modulates chimeric mRNAs export	Promotes leukemia progression	75
Xist	METTL14	METTL14-mediated m^{6}A modification down-regulates Xist	Suppresses colorectal cancer metastasis	76
RP11	METTL3/ALKBH5	m^{6}A modification up-regulates RP11 expression	Promotes cancer cell metastasis	78
NEAT1	METTL3	RNA m^{6}A-methylated NEAT1 facilitates oncogenic complex	Promotes bone metastasis of prostate cancer	79
FAM225A	/	FAM225A modulate ITGB3 expression by binding to miR-590-3p and miR-1275	Promotes nasopharyngeal carcinoma tumorigenesis and metastasis	80
THAP7-AS1	METTL3, IGF2BP1	METTL3-mediated m^{6}A methylation stabilizes THAP7-AS1 by IGF2BP1	Promotes gastric cancer	81
SNHG17	METTL3	METTL3 increases the m^{6}A methylation and stability of SNHG17	Promotes gefitinib resistance in lung adenocarcinoma	82
LINREP	METTL3	METTL3 knockdown decreases the m^{6}A methylation level and RNA expression level of LINREP	Promotes glioblastoma multiforme progression	83
RMRP	METTL3	RNA m^{6}A methylation in RMRP enhances its stability	Facilitates non-small cell lung cancer progression	84
DIAPH1-AS1	WTAP	RNA m^{6}A methylation in DIAPH1-AS1 enhances its stability	Facilitates nasopharyngeal carcinoma growth and metastasis	85
ANRIL	METTL3	METTL3-mediated m^{6}A methylation elevation takes a crucial role in the occurrence of SRSF3-mediated ANRIL splicing events	Promotes gemcitabine resistance in pancreatic cancer	86
RAB11B-AS1	METTL16	METTL16-mediated m^{6}A methylation on lncRNA RAB11B-AS1 and decreases its stability	Suppresses the progression of hepatocellular carcinoma	87
ZNRD1-AS1	YTHDC2	YTHDC2 down-regulates ZNRD1-AS1	Suppresses the progression of lung cancer	88
GAS5	YTHDF3	YTHDF3 facilitates m^{6}A-modified GAS5 degradation	Suppresses the progression of colorectal cancer	89
NORAD	WTAP, YTHDF2	WTAP-mediated m^{6}A methylation on lncRNA NORAD promotes the degradation of lncRNA NORAD in a YTHDF2-dependent manner	Inhibits nucleus pulposus cells senescence	90
mmu-lncRNA 121686/hsa-lncRNA 520657	METTL3	METTL3 knockdown decreases the m^{6}A methylation level of mmu-lncRNA 121686/hsa-lncRNA 520657	Aggravates acute kidney injury	91
FENDRR	YTHDC1	YTHDC1 can decrease m^{6}A-modified FENDRR's stability	Inhibits hypoxic pulmonary artery endothelial cell pyroptosis	92

Table 2 (*continued*)

LncRNAs	RNA m^{6}A effectors	Mechanism	Biological function	References
The effect of lncRNA on RNA m6A methylation				
DMDRMR	IGF2BP3	DMDRMR enhances the activity of IGF2BP3 to regulate target genes	Facilitates tumor growth and metastasis	93
MALAT1	IGF2BP2	MALAT1 up-regulates IGF2BP2 and enhances MYC expression via m^{6}A modification recognition	Promotes thyroid cancer progression	94

circRNAs, which followed a non-canonical translation pathway for protein synthesis, was positively regulated by the m^{6}A levels. Specifically, this m^{6}A-driven translation was initiated by the binding of YTHDF3 and translation initiation factors eIF4G2 and eIF3A.[98] Circ-ZNF609 was the most well-studied translated circRNA, which was translated into a protein in response to heat shock.[103] RNA m^{6}A regulates circ-ZNF609 translation via YTHDF3 and eIF4G2.[99] Recently, our group reported that down-regulation of circ-ZNF609 could promote heart repair.[104] Mechanistically, m^{6}A modified-circ-ZNF609 was reported to exert its regulatory role via regulating another m^{6}A modified mRNA, *Yap* expression, demonstrating the critical role of m^{6}A modification in circRNA regulatory function.[104] M^{6}A-modified circRNA circE7 was also identified to be bound to polysomes and translated to E7 oncoprotein, which was essential for the transforming potential of human papillomaviruses.[105] In eukaryotic cells, apart from the canonical cap-dependent translation initiation machinery, non-canonical translation mechanisms have been detected and proposed to be associated with stress responses.[106] The fundamental role of m^{6}A-driven translation of circRNAs remains largely unknown, and any further investigations on m^{6}A modifications and circRNA translation, as well as their regulatory roles correlated with human health, would be of great significance.

CircRNAs are more stable and have a longer half-life compared with their parent linear mRNAs due to their cyclized structure, along with the fact that circRNA degradation mechanisms are more complex and specific (Fig. 5). CircCDR1 can be cleaved and degraded in a miRNA-dependent manner.[107] During innate immune responses,

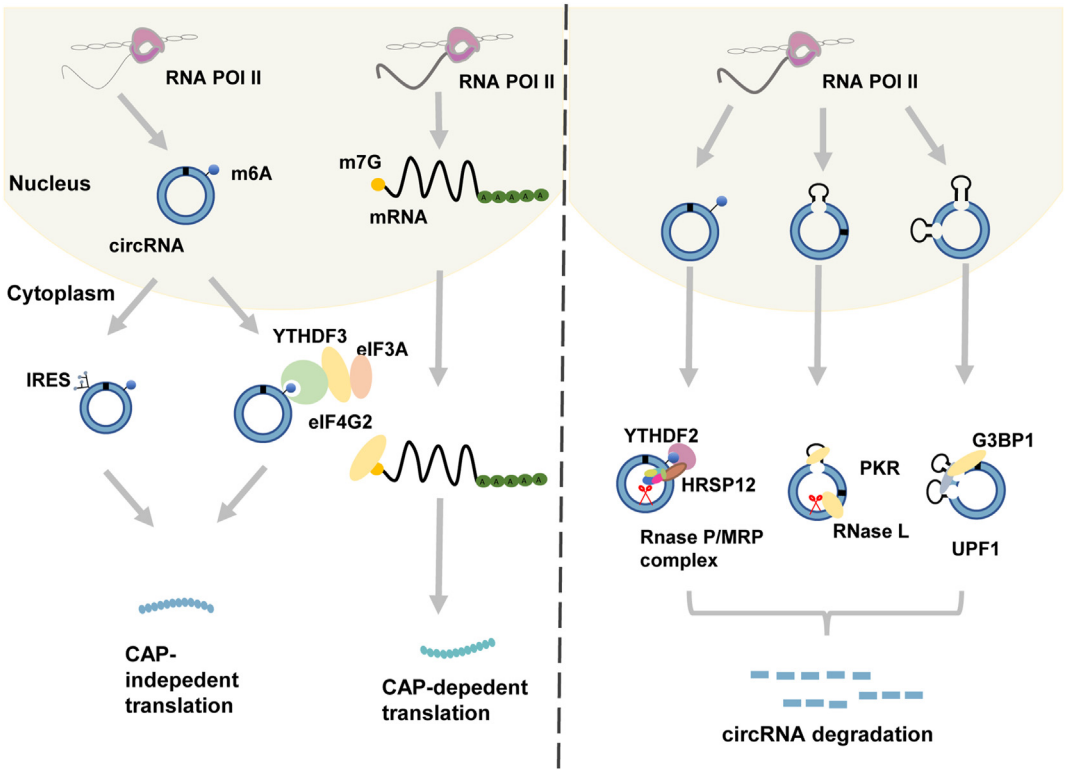

Figure 5 The regulation of circRNAs by RNA m^{6}A modification. RNA m^{6}A methylation regulates the translation and degradation of circRNAs.

circRNAs have been observed to be degraded by endoribonuclease RNase L.[108] Additionally, RNA m^{6}A methylation participates in the regulation of m^{6}A-methylated circRNA decay.[109] Usually, m^{6}A containing circRNAs are recognized by YTHDF2 in an HRSP12-dependent way, and therefore, degraded by RNase P/MRP. In addition, highly structured circRNA degradation can also be mediated by UPF1 and its binding partner G3BP1.[110] In fact, RNA m^{6}A-binding proteins YTHDFs are important for stress granule formation.[111] Because G3BP1 is the marker gene of stress granule formation, RNA m^{6}A modification might also contribute to structure-mediated circRNA decay. Therefore, other potential regulatory mechanisms in which RNA m^{6}A modification is involved in circRNA decay are certainly worth exploring.

Aberrant expression of circRNA is closely related to many diseases.[96,112,113] Also, dysregulation of m^{6}A RNA modifications has been observed in various pathological processes. Despite a limited number of investigations on the function of m^{6}A-methylated circRNAs in diseases, a certain level of understanding regarding this process has been reached (Fig. 6). Endogenous m^{6}A-containing circRNA can be recognized by YTHDF2 and inhibit innate immunity.[100] Also, circRNAs with m^{6}A modification exerted crucial roles during cancer progression. circNSUN2 has been found to be up-regulated in colorectal carcinoma patients with liver metastasis, wherein the RNA m^{6}A modification of circNSUN2 was seen to promote its cytoplasmic export, and consequently, stabilized *Hmga2* mRNA to facilitate the aggressiveness of cancer.[114] Similarly, another circRNA circ3823 promoted colorectal cancer progression via sponging miR-30c-5p. Mechanically, the RNA m^{6}A modification that occurred in circ3823, regulated its decay via YTHDF3 and ALKBH5.[115] Besides, the expression of circCUX1 was observed to be increased in head and neck squamous cell carcinoma patients resistant to radiotherapy. Here, METTL3-mediated m^{6}A modification on circCUX1 stabilized its expression and predicted a poor survival outcome.[116] A similar phenomenon was observed with circRNA-SORE, circMDK, and circCCDC134.[117–119] Elevated RNA m^{6}A level in circRNA-SORE increased its stability and sustained sorafenib resistance in hepatocellular carcinoma.[117] Also, IGF2BP1 stabilized m^{6}A-methylated circMDK (hsa_circ_0095,868) and promoted tumorigenesis in hepatocellular carcinoma.[118] ALKBH5-mediated m^{6}A modification on circCCDC134 controlled its stability and can enhance cervical cancer metastasis in a YTHDF2-dependent manner.[119] In addition to direct methylation on circRNAs, RNA m^{6}A methylation also occurred in the flanking sequences of circ1662 affecting its biogenesis in colorectal cancer.[120] Moreover, circRNAs took part in the dynamic regulation of m^{6}A by altering the activity or expression of RNA m^{6}A effectors. CircPTPRA was identified to disrupt the m^{6}A-modified RNA recognition of IGF2BP1 by interacting with IGF2BP1 KH domains to inhibit bladder cancer progression.[121] CircZBTB20 enhanced the interaction between RNA m^{6}A demethylases ALKBH5 and *Nr4a1* mRNA to maintain group 3 innate lymphoid cell homeostasis.[122] CircEZH2 increased the stability of m^{6}A reader IGF2BP2 and aggravated colorectal cancer.[123] CircPDE5A bound to WTAP and inhibited WTAP-mediated m^{6}A modification of *Eif3c* mRNA to suppress prostate cancer metastasis.[124] Notably, circSTAG1 ameliorated depressive behavior in mice by decreasing the translocation of ALKBH5 to the nucleus and further promoted the fatty acid amide hydrolase mRNA m^{6}A methylation.[125] Another m^{6}A demethylase, FTO, directly bound to circRAB11FIP1 facilitating its mRNA expression in ovarian cancer.[126] Along with reader and demethylases,

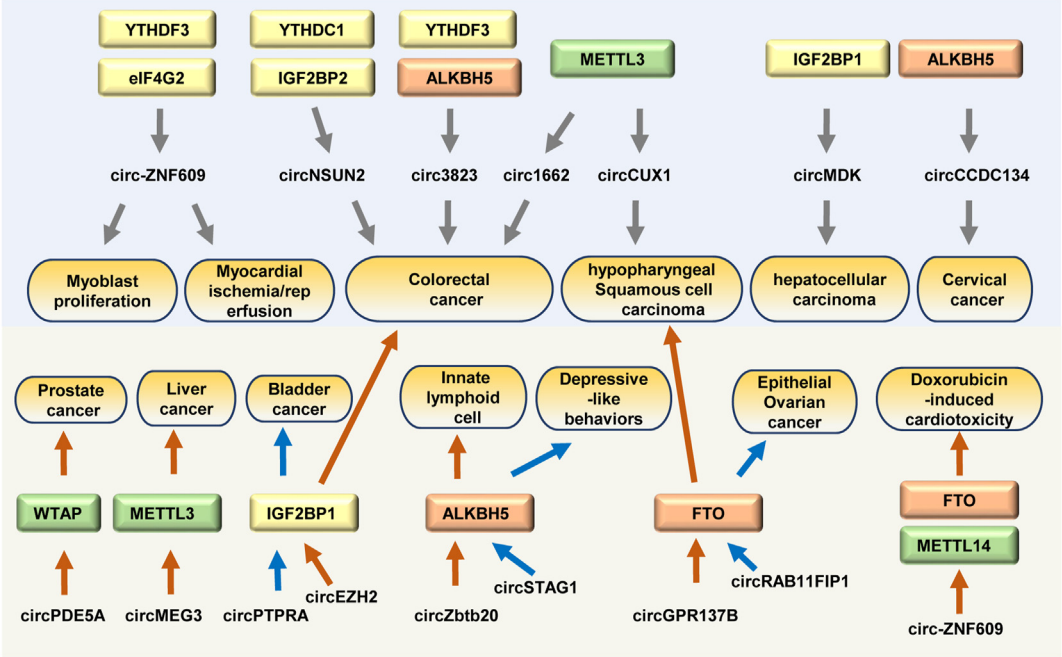

Figure 6 Mutual regulation between RNA m^{6}A and circRNAs in human diseases. Aberrant expression of m^{6}A-methylated circRNAs in human diseases. circRNAs are also involved in the dynamic regulation of RNA m^{6}A.

Table 3 Mutual regulation between RNA m^{6}A modification and circRNAs.

circRNAs	RNA m^{6}A effectors	Mechanism	Biological function	References
The effect of RNA m^{6}A methylation on circRNA				
circ-ZNF609	YTHDF3, eIF4G2	m^{6}A regulates circZNF609 translation via YTHDF3 and eIF4G2	Regulates myoblast proliferation	98, 99, 103
circ-ZNF609	YTHDF3	m^{6}A-modified circ-ZNF609 regulates the expression of m^{6}A-modified *Yap* via binding to YTHDF3	Regulates cardiomyocyte survival	104
circE7	/	m^{6}A-modified circE7 translated to produce E7 oncoprotein	Highly associated with human papillomaviruses	105
circNSUN2	YTHDC1, IGF2BP2	m^{6}A modification of circNSUN2 increases export to the cytoplasm and enhances the stability of HMGA2 mRNA via IGF2BP2	Promotes colorectal cancer metastasis progression	114
circ3823	YTHDF3, ALKBH5	m^{6}A modification presents in circ3823 and regulates its decay	Promotes colorectal cancer progression	115
circCUX1	METTL3	METTL3 mediated m^{6}A methylation of circCUX1 and stabilizes its expression	Predicts a poor survival outcome of hypopharyngeal squamous cell carcinoma	116
circRNA-SORE	/	m^{6}A modification of circRNA-SORE increases its stability	Maintenance of sorafenib resistance in hepatocellular carcinoma	117
circMDK	IGF2BP1	IGF2BP1 stabilizes m^{6}A-methylated circMDK	Promotes tumorigenesis in hepatocellular carcinoma	118
circCCDC134	ALKBH5	ALKBH5-mediated m^{6}A modification on circCCDC134 controlled its stability	Enhances cervical cancer metastasis	119
circ1662	METTL3	METTL3 induces circ1662 expression by binding its flanking sequences and installing m^{6}A modifications	Promotes colorectal cancer metastasis	120
The effect of circRNA on RNA m6A methylation				
circPTPRA	IGF2BP1	CircPTPRA interacts with IGF2BP1 KH domains to disturb IGF2BP1's m^{6}A-modified RNA recognition	Suppresses bladder cancer progression	121
circZbtb20	ALKBH5	circZbtb20 enhances the interaction of *Alkbh5* with *Nr4a1* mRNA	Maintenance of group 3 innate lymphoid cells homeostasis	122
circEZH2	IGF2BP2	circEZH2 increases the stability of m^{6}A reader IGF2BP2	Aggravates colorectal cancer	123
circPDE5A	WTAP	circPDE5A binds to WTAP and inhibits WTAP-mediated m^{6}A modification of *Eif3c* mRNA	Suppresses prostate cancer metastasis	124
circSTAG1	ALKBH5	circSTAG1 captures ALKBH5 and decreases the translocation of ALKBH5 into nucleus, leading to ALKBH5′S targeted mRNA degradation	Attenuates depressive-like behaviors in mice	125
CircRAB11FIP1	FTO	circRAB11FIP1 directly binds to *Fto* mRNA and promotes its expression	CircRAB11FIP1 induces autophagy accelerating proliferation and invasion in epithelial ovarian cancer	126
CircMEG3	METTL3	CircMEG3 inhibits METTL3 expression	Inhibits human liver cancer growth	127

(*continued on next page*)

Table 3 (*continued*)

circRNAs	RNA m^{6}A effectors	Mechanism	Biological function	References
CircGPR137B	FTO	m^{6}A-demethylation promotes circGPR137B and circGPR137B up-regulates FTO	Suppresses hepatocellular carcinoma	129
Circ-ZNF609	METTL14, FTO	m^{6}A-methylation promotes circ-ZNF609 and circ-ZNF609 inhibits FTO	Aggravates doxorubicin-induced cardiotoxicity	128

m^{6}A methyltransferase METTL3 was found to be suppressed by circMEG3. Increased expression of circMEG3 was observed to act as an anti-tumor factor in human liver cancer.[127] Moreover, circRNA-m^{6}A modification can form a feedback loop to mutually regulate each other and exert function in cells.[128,129] M^{6}A-modified circGPR137B inhibited hepatocellular carcinoma via forming a feedback loop with FTO.[129] Similarly, RNA m^{6}A-regulated circ-ZNF609 alleviated doxorubicin-induced cardiotoxicity by promoting FTO expression.[128] Collectively, these studies implicate that the regulatory interaction between RNA m^{6}A modification and circRNAs could be highly associated with human health, and future research in this direction could lead to better therapeutic intervention for many diseases (Table 3).

Therapeutic strategies to modulate the RNA m^{6}A regulators

RNA modification plays important roles in normal physiological conditions and various diseases. Targeting epigenetic regulators has provided new therapeutic strategies for human diseases.[130,131] Like histone modification and DNA methylation, small molecules targeting RNA m^{6}A regulators have been developed. Rhein was the first identified FTO small molecule inhibitor, and rhein caused the increase of mRNA m^{6}A levels in cells.[132] However, rhein bound to the nucleic acid-binding site and demonstrated little selectivity for the AlkB subfamily. Using a high-throughput fluorescence polarization assay, meclofenamic acid has been discovered to inhibit RNA m^{6}A demethylase FTO.[133] Different from the 2-oxoglutarate-tethering screen strategy, meclofenamic acid specifically inhibits FTO over ALKBH5, which would provide opportunities for specific targeting FTO for biological and therapeutic studies. Other FTO inhibitors, FB23 and FB23-2, displayed therapeutic effects in acute myeloid leukemia.[134] In addition to targeting RNA m^{6}A demethylase, small molecule targeting RNA m^{6}A methyltransferase inhibitors were also developed. S-adenosylhomocysteine (SAH) demonstrated inhibitory effects on METTL3-METTL14 complex.[135] UZH1a was a METTL3 inhibitor with high—nanomolar activity, UZH1a treatment reduced cellular m^{6}A level and induced acute myeloid leukemia MOLM-13 cell apoptosis.[136] Besides, STM2457, a bioavailable inhibitor of METTL3, has been characterized and developed as a therapeutic strategy against acute myeloid leukemia.[137] Notably, STM2457 was also the first known small molecule inhibitor of an RNA methyltransferase which demonstrated *in vivo* activity and therapeutic efficacy. In addition, inhibitors that were targeted to RNA m^{6}A binding proteins can also provide new therapeutic opportunities for diseases. Tegaserod has been identified as a specific YTHDF1 inhibitor and Tegaserod treatment inhibited acute myeloid leukemia progression via YTHDF1.[138] Despite some scientific advances, understanding epigenetic therapies for disease treatment is only just beginning. Further studies to develop new inhibitors targeting RNA m^{6}A regulators with improved specificity and much more favorable pharmacokinetic profiles would provide better opportunities for RNA m^{6}A regulators-based therapeutic interventions.

Conclusions and perspectives

In the past few years, thanks to the tremendous progress of new technologies, precise detection of m^{6}A-depositions and efficient m^{6}A methylation installation systems have been developed.[139—141] An increasing number of investigations have demonstrated the important roles of m^{6}A RNA modification in physiological and pathological processes. Recently, more attention has been bestowed on studying the regulation of m^{6}A deposition on RNA, especially in the context of ncRNAs. Studying m^{6}A RNA modifications on ncRNAs is undoubtedly of great importance specifically to deepen our understanding of their biological roles and clinical implications.

Though tremendous progress has been made in recent times, to better uncover this RNA m^{6}A-ncRNAs epigenetic regulation network, several questions need to be further explored. First, the understanding of the underlying mechanisms regarding the m^{6}A modification and ncRNAs remains limited. This is more relevant, especially in a specific context, wherein the RNA m^{6}A modification and ncRNAs regulation always exhibit cell- or tissue-specific interaction. Future studies to address the cell-type specific regulation under a particular context (disease or normal) represent an important area of investigation. Second, RNA m^{6}A modifications and ncRNA dysregulation are closely associated with many human diseases. However, since most of the elaborate studies are still focused on the field of cancer, there is a growing need to explore the biological functions and clinical implications of RNA m^{6}A modifications in other diseases. Future efforts to develop new sequencing and detection technologies for not only RNA m^{6}A modification but also ncRNAs, especially lncRNAs and circRNA, would surely move this field forward and provide greater insight into understanding exact mechanisms as well as a potential strategy for the treatment of human diseases.

While there have been reviews summarizing the research progress of RNA m^{6}A over the past few years, it is important to note that our understanding of RNA m^{6}A and its potential applications in medical research is constantly evolving with the rapid advancements in literature. In this present review, we summarized the latest information about the mutual regulation between RNA m^{6}A modification and ncRNAs, with a specific focus on miRNAs, lncRNAs, and circRNAs. Also, we have discussed the challenges of m^{6}A-containing ncRNAs and RNA m^{6}A as therapeutic targets in human diseases and their future perspective in translational roles. The growing understanding of RNA m^{6}A modification has led to the development of RNA m^{6}A -based therapeutic interventions. RNA m^{6}A-modified genes and their regulatory factors are expected to be potential therapeutic targets. One of the attractive areas is the development of new inhibitors targeting m^{6}A-regulatory factors, including RNA m^{6}A methyltransferase, demethylase, and specific binding protein, and exploration of the relationship between enzyme/reader inhibition and disease phenotypes. Considering the complexity and global effects of RNA m^{6}A methylation regulation and recognition, comprehensive experiments and population-based data are required before the therapeutic potential of those inhibitors can be clinically evaluated. With the rapid progresses in gene editing technologies, gene editing-based technologies on RNA modifications have been designed and remarkable progress has been achieved.[142,143] Using gene editing technology to regulate specific target transcript's m^{6}A methylation level is another promising therapeutic strategy for RNA m^{6}A -based therapeutic interventions. Further investigation to apply gene-editing based- RNA m^{6}A control in living organisms might offer a precise tool to regulate RNA m^{6}A modification with high efficiency and specificity.

Author contributions

All authors contributed to the design and interpretation of this work. Gui-e Xu: conceptualization, data curation, methodology, writing-original draft. Xuan Zhao: conceptualization, data curation, methodology. Guoping Li: conceptualization, writing-reviewing, and editing. Priyanka Gokulnath: conceptualization, writing-reviewing, and editing. Lijun Wang: conceptualization, supervision, funding acquisition, writing-original draft, writing-reviewing, and editing. Junjie Xiao: conceptualization, supervision, project administration, funding acquisition, writing-reviewing, and editing. All authors read and approved the final version of the manuscript.

Conflict of interests

The authors declare no competing interests.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 82020108002 & 82225005 to JJ Xiao, 82270291 to LJ Wang), the Science and Technology Commission of Shanghai, China (No. 23410750100, 20DZ2255400 & 21XD1421300 to JJ Xiao), and the Natural Science Foundation of Shanghai, China (No. 23ZR1423000 to LJ Wang).

References

1. Wu G, Zhang X, Gao F. The epigenetic landscape of exercise in cardiac health and disease. *J Sport Health Sci*. 2021;10(6):648–659.
2. Nishiyama A, Nakanishi M. Navigating the DNA methylation landscape of cancer. *Trends Genet*. 2021;37(11):1012–1027.
3. Wu Q, Schapira M, Arrowsmith CH, Barsyte-Lovejoy D. Protein arginine methylation: from enigmatic functions to therapeutic targeting. *Nat Rev Drug Discov*. 2021;20(7):509–530.
4. Bhat KP, Ümit Kaniskan H, Jin J, Gozani O. Epigenetics and beyond: targeting writers of protein lysine methylation to treat disease. *Nat Rev Drug Discov*. 2021;20(4):265–286.
5. Sun L, Zhang H, Gao P. Metabolic reprogramming and epigenetic modifications on the path to cancer. *Protein Cell*. 2022;13(12):877–919.
6. Sánchez-Vásquez E, Alata Jimenez N, Vázquez NA, Strobl-Mazzulla PH. Emerging role of dynamic RNA modifications during animal development. *Mech Dev*. 2018;154:24–32.
7. Yang Y, Hsu PJ, Chen YS, Yang YG. Dynamic transcriptomic m^{6}A decoration: writers, erasers, readers and functions in RNA metabolism. *Cell Res*. 2018;28(6):616–624.
8. Wu S, Zhang S, Wu X, Zhou X. m^{6}A RNA methylation in cardiovascular diseases. *Mol Ther*. 2020;28(10):2111–2119.
9. Livneh I, Moshitch-Moshkovitz S, Amariglio N, Rechavi G, Dominissini D. The m^{6}A epitranscriptome: transcriptome plasticity in brain development and function. *Nat Rev Neurosci*. 2020;21(1):36–51.
10. Chen YS, Ouyang XP, Yu XH, et al. N6-adenosine methylation (m^{6}A) RNA modification: an emerging role in cardiovascular diseases. *J Cardiovasc Transl Res*. 2021;14(5):857–872.
11. Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in development and disease: background, mechanisms, and therapeutic approaches. *Physiol Rev*. 2016;96(4):1297–1325.
12. Jiang X, Liu B, Nie Z, et al. The role of m6A modification in the biological functions and diseases. *Signal Transduct Targeted Ther*. 2021;6(1):74.
13. Kim J, Lee G. Metabolic control of m6A RNA modification. *Metabolites*. 2021;11(2):80.
14. Huang H, Weng H, Chen J. The biogenesis and precise control of RNA m^{6}A methylation. *Trends Genet*. 2020;36(1):44–52.
15. Desrosiers R, Friderici K, Rottman F. Identification of methylated nucleosides in messenger RNA from Novikoff hepatoma cells. *Proc Natl Acad Sci U S A*. 1974;71(10):3971–3975.
16. Desrosiers RC, Friderici KH, Rottman FM. Characterization of Novikoff hepatoma mRNA methylation and heterogeneity in the methylated 5' terminus. *Biochemistry*. 1975;14(20):4367–4374.
17. Yue Y, Liu J, He C. RNA N6-methyladenosine methylation in post-transcriptional gene expression regulation. *Genes Dev*. 2015;29(13):1343–1355.
18. Sun T, Wu R, Ming L. The role of m6A RNA methylation in cancer. *Biomed Pharmacother*. 2019;112:108613.
19. Wang H, Bei Y, Huang P, et al. Inhibition of miR-155 protects against LPS-induced cardiac dysfunction and apoptosis in mice. *Mol Ther Nucleic Acids*. 2016;5:e374.
20. Horiuchi K, Kawamura T, Iwanari H, et al. Identification of Wilms' tumor 1-associating protein complex and its role in

alternative splicing and the cell cycle. *J Biol Chem*. 2013; 288(46):33292—33302.
21. Liu J, Yue Y, Han D, et al. A METTL3-METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. *Nat Chem Biol*. 2014;10(2):93—95.
22. Ping XL, Sun BF, Wang L, et al. Mammalian WTAP is a regulatory subunit of the RNA N6-methyladenosine methyltransferase. *Cell Res*. 2014;24(2):177—189.
23. Patil DP, Chen CK, Pickering BF, et al. m^{6}A RNA methylation promotes XIST-mediated transcriptional repression. *Nature*. 2016;537(7620):369—373.
24. Schwartz S, Mumbach MR, Jovanovic M, et al. Perturbation of m6A writers reveals two distinct classes of mRNA methylation at internal and 5' sites. *Cell Rep*. 2014;8(1):284—296.
25. Wen J, Lv R, Ma H, et al. Zc3h13 regulates nuclear RNA m^{6}A methylation and mouse embryonic stem cell self-renewal. *Mol Cell*. 2018;69(6):1028—1038. e6.
26. Zheng G, Dahl JA, Niu Y, et al. ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. *Mol Cell*. 2013;49(1):18—29.
27. Jia G, Fu Y, Zhao X, et al. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. *Nat Chem Biol*. 2011;7(12):885—887.
28. Zheng G, Dahl JA, Niu Y, et al. ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. *Mol Cell*. 2013;49(1):18—29.
29. Ueda Y, Ooshio I, Fusamae Y, et al. AlkB homolog 3-mediated tRNA demethylation promotes protein synthesis in cancer cells. *Sci Rep*. 2017;7:42271.
30. Chen Z, Qi M, Shen B, et al. Transfer RNA demethylase ALKBH3 promotes cancer progression via induction of tRNA-derived small RNAs. *Nucleic Acids Res*. 2019;47(5):2533—2545.
31. Roundtree IA, Evans ME, Pan T, He C. Dynamic RNA modifications in gene expression regulation. *Cell*. 2017;169(7): 1187—1200.
32. Theler D, Dominguez C, Blatter M, Boudet J, Allain FHT. Solution structure of the YTH domain in complex with N6-methyladenosine RNA: a reader of methylated RNA. *Nucleic Acids Res*. 2014;42(22):13911—13919.
33. Huang H, Weng H, Sun W, et al. Recognition of RNA N6-methyladenosine by IGF2BP proteins enhances mRNA stability and translation. *Nat Cell Biol*. 2018;20(3):285—295.
34. Alarcón CR, Goodarzi H, Lee H, Liu X, Tavazoie S, Tavazoie SF. HNRNPA2B1 is a mediator of m^{6}A-dependent nuclear RNA processing events. *Cell*. 2015;162(6):1299—1308.
35. Wang X, Zhao BS, Roundtree IA, et al. N(6)-methyladenosine modulates messenger RNA translation efficiency. *Cell*. 2015; 161(6):1388—1399.
36. Wang X, Lu Z, Gomez A, et al. N6-methyladenosine-dependent regulation of messenger RNA stability. *Nature*. 2014; 505(7481):117—120.
37. Du H, Zhao Y, He J, et al. YTHDF$_2$ destabilizes m(6)A-containing RNA through direct recruitment of the CCR4-NOT deadenylase complex. *Nat Commun*. 2016;7:12626.
38. Shi H, Wang X, Lu Z, et al. YTHDF$_3$ facilitates translation and decay of N^6-methyladenosine-modified RNA. *Cell Res*. 2017; 27(3):315—328.
39. Xiao W, Adhikari S, Dahal U, et al. Nuclear m^{6}A reader YTHDC1 regulates mRNA splicing. *Mol Cell*. 2016;61(4):507—519.
40. Roundtree IA, Luo GZ, Zhang Z, et al. YTHDC1 mediates nuclear export of N6-methyladenosine methylated mRNAs. *Elife*. 2017;6:e31311.
41. Hsu PJ, Zhu Y, Ma H, et al. Ythdc2 is an N^6-methyladenosine binding protein that regulates mammalian spermatogenesis. *Cell Res*. 2017;27(9):1115—1127.
42. Müller S, Glaß M, Singh AK, et al. IGF$_2$BP$_1$ promotes SRF-dependent transcription in cancer in a m6A- and miRNA-dependent manner. *Nucleic Acids Res*. 2019;47(1):375—390.
43. Wang S, Chim B, Su Y, et al. Enhancement of LIN28B-induced hematopoietic reprogramming by IGF$_2$BP$_3$. *Genes Dev*. 2019; 33(15—16):1048—1068.
44. Liu N, Dai Q, Zheng G, He C, Parisien M, Pan T. N(6)-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. *Nature*. 2015;518(7540):560—564.
45. Liu N, Zhou KI, Parisien M, Dai Q, Diatchenko L, Pan T. N6-methyladenosine alters RNA structure to regulate binding of a low-complexity protein. *Nucleic Acids Res*. 2017;45(10): 6051—6063.
46. Bartel DP. microRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004;116(2):281—297.
47. Wang L, Lv Y, Li G, Xiao J. microRNAs in heart and circulation during physical exercise. *J Sport Health Sci*. 2018;7(4): 433—441.
48. Liu Q, Chen L, Liang X, et al. Exercise attenuates angiotensinII-induced muscle atrophy by targeting PPARγ/miR-29b. *J Sport Health Sci*. 2022;11(6):696—707.
49. Lou J, Wu J, Feng M, et al. Exercise promotes angiogenesis by enhancing endothelial cell fatty acid utilization via liver-derived extracellular vesicle miR-122-5p. *J Sport Health Sci*. 2022;11(4):495—508.
50. Wang H, Deng Q, Lv Z, et al. N6-methyladenosine induced miR-143-3p promotes the brain metastasis of lung cancer via regulation of VASH1. *Mol Cancer*. 2019;18(1):181.
51. Alarcón CR, Lee H, Goodarzi H, Halberg N, Tavazoie SF. N6-methyladenosine marks primary microRNAs for processing. *Nature*. 2015;519(7544):482—485.
52. Han J, Wang JZ, Yang X, et al. METTL3 promote tumor proliferation of bladder cancer by accelerating pri-miR221/222 maturation in m6A-dependent manner. *Mol Cancer*. 2019; 18(1):110.
53. Yan G, Yuan Y, He M, et al. m^{6}A methylation of precursor-miR-320/RUNX2 controls osteogenic potential of bone marrow-derived mesenchymal stem cells. *Mol Ther Nucleic Acids*. 2020;19:421—436.
54. Zhang J, Bai R, Li M, et al. Excessive miR-25-3p maturation via N^6-methyladenosine stimulated by cigarette smoke promotes pancreatic cancer progression. *Nat Commun*. 2019;10(1): 1858.
55. Peng W, Li J, Chen R, et al. Upregulated METTL3 promotes metastasis of colorectal Cancer via miR-1246/SPRED2/MAPK signaling pathway. *J Exp Clin Cancer Res*. 2019;38(1):393.
56. Wang J, Ishfaq M, Xu L, Xia C, Chen C, Li J. METTL3/m^{6}A/-miRNA-873-5p attenuated oxidative stress and apoptosis in colistin-induced kidney injury by modulating Keap1/Nrf2 pathway. *Front Pharmacol*. 2019;10:517.
57. Chen X, Xu M, Xu X, et al. METTL14 suppresses CRC progression via regulating N6-methyladenosine-dependent primary miR-375 processing. *Mol Ther*. 2019;28:599—612.
58. Ma JZ, Yang F, Zhou CC, et al. METTL14 suppresses the metastatic potential of hepatocellular carcinoma by modulating N$_6$-methyladenosine-dependent primary microRNA processing. *Hepatology*. 2016;65(2):529—543.
59. Shah A, Rashid F, Awan HM, et al. The DEAD-box RNA helicase DDX3 interacts with m6A RNA demethylase ALKBH5. *Stem Cell Int*. 2017;2017:8596135.
60. Zhu H, Gan X, Jiang X, Diao S, Wu H, Hu J. ALKBH5 inhibited autophagy of epithelial ovarian cancer through miR-7 and BCL-2. *J Exp Clin Cancer Res*. 2019;38(1):163.
61. Berulava T, Rahmann S, Rademacher K, Klein-Hitpass L, Horsthemke B. N6-adenosine methylation in MiRNAs. *PLoS One*. 2015;10(2):e0118438.
62. Qian B, Wang P, Zhang D, Wu L. m6A modification promotes miR-133a repression during cardiac development and hypertrophy via IGF$_2$BP$_2$. *Cell Death Dis*. 2021;7(1):157.
63. Yang Z, Li J, Feng G, et al. microRNA-145 modulates *N*^{6}-methyladenosine levels by targeting the 3'-untranslated

mRNA region of the N^6-methyladenosine binding YTH domain family 2 protein. *J Biol Chem*. 2017;292(9):3614—3623.
64. He H, Wu W, Sun Z, Chai L. miR-4429 prevented gastric cancer progression through targeting METTL3 to inhibit m^{6}A-caused stabilization of SEC62. *Biochem Biophys Res Commun*. 2019; 517(4):581—587.
65. Xu C, Yuan B, He T, Ding B, Li S. Prognostic values of YTHDF$_1$ regulated negatively by mir-3436 in Glioma. *J Cell Mol Med*. 2020;24(13):7538—7549.
66. Lara-Pezzi E. Understanding cardiac physiological hypertrophy in a LncRNA way. *J Cardiovasc Transl Res*. 2022;15(1): 3—4.
67. Sun J, Wang R, Chao T, Wang C. Long noncoding RNAs involved in cardiomyocyte apoptosis triggered by different stressors. *J Cardiovasc Transl Res*. 2022;15(3):588—603.
68. Liu N, Parisien M, Dai Q, Zheng G, He C, Pan T. Probing N6-methyladenosine RNA modification status at single nucleotide resolution in mRNA and long noncoding RNA. *RNA*. 2013; 19(12):1848—1856.
69. Dominissini D, Moshitch-Moshkovitz S, Schwartz S, et al. Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq. *Nature*. 2012;485(7397):201—206.
70. Huang H, Weng H, Chen J. m^{6}A modification in coding and non-coding RNAs: roles and therapeutic implications in cancer. *Cancer Cell*. 2020;37(3):270—288.
71. Chu C, Zhang QC, da Rocha ST, et al. Systematic discovery of Xist RNA binding proteins. *Cell*. 2015;161(2):404—416.
72. Moindrot B, Cerase A, Coker H, et al. A pooled shRNA screen identifies Rbm15, spen, and wtap as factors required for xist RNA-mediated silencing. *Cell Rep*. 2015;12(4):562—572.
73. Chang YZ, Chai RC, Pang B, et al. METTL3 enhances the stability of MALAT1 with the assistance of HuR via m6A modification and activates NF-κB to promote the malignant progression of IDH-wildtype glioma. *Cancer Lett*. 2021;511: 36—46.
74. Wang X, Liu C, Zhang S, et al. N^6-methyladenosine modification of MALAT1 promotes metastasis via reshaping nuclear speckles. *Dev Cell*. 2021;56(5):702—715. e8.
75. Chen ZH, Chen TQ, Zeng ZC, et al. Nuclear export of chimeric mRNAs depends on an lncRNA-triggered autoregulatory loop in blood malignancies. *Cell Death Dis*. 2020;11:566.
76. Yang X, Zhang S, He C, et al. METTL14 suppresses proliferation and metastasis of colorectal cancer by down-regulating oncogenic long non-coding RNA XIST. *Mol Cancer*. 2020;19(1): 46.
77. Nesterova TB, Wei G, Coker H, et al. Systematic allelic analysis defines the interplay of key pathways in X chromosome inactivation. *Nat Commun*. 2019;10(1):3129.
78. Wu Y, Yang X, Chen Z, et al. m^{6}A-induced lncRNA RP11 triggers the dissemination of colorectal cancer cells via upregulation of Zeb1. *Mol Cancer*. 2019;18(1):87.
79. Wen S, Wei Y, Zen C, Xiong W, Niu Y, Zhao Y. Long non-coding RNA NEAT1 promotes bone metastasis of prostate cancer through N6-methyladenosine. *Mol Cancer*. 2020;19(1):171.
80. Zheng ZQ, Li ZX, Zhou GQ, et al. 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*. 2019;79(18): 4612—4626.
81. Liu HT, Zou YX, Zhu WJ, et al. lncRNA THAP7-AS1, transcriptionally activated by SP1 and post-transcriptionally stabilized by METTL3-mediated m6A modification, exerts oncogenic properties by improving CUL4B entry into the nucleus. *Cell Death Differ*. 2022;29(3):627—641.
82. Zhang H, Wang SQ, Wang L, et al. m6A methyltransferase METTL3-induced lncRNA SNHG17 promotes lung adenocarcinoma gefitinib resistance by epigenetically repressing LATS2 expression. *Cell Death Dis*. 2022;13(7):657.
83. Ji X, Liu Z, Gao J, et al. N^6-Methyladenosine-modified lncRNA LINREP promotes glioblastoma progression by recruiting the PTBP1/HuR complex. *Cell Death Differ*. 2023;30(1):54—68.
84. Yin H, Chen L, Piao S, et al. M6A RNA methylation-mediated RMRP stability renders proliferation and progression of non-small cell lung cancer through regulating TGFBR1/SMAD2/SMAD3 pathway. *Cell Death Differ*. 2023;30(3):605—617.
85. Li ZX, Zheng ZQ, Yang PY, et al. WTAP-mediated m^{6}A modification of lncRNA DIAPH1-AS1 enhances its stability to facilitate nasopharyngeal carcinoma growth and metastasis. *Cell Death Differ*. 2022;29(6):1137—1151.
86. Wang ZW, Pan JJ, Hu JF, et al. SRSF3-mediated regulation of N6-methyladenosine modification-related lncRNA ANRIL splicing promotes resistance of pancreatic cancer to gemcitabine. *Cell Rep*. 2022;39(6):110813.
87. Dai YZ, Liu YD, Li J, et al. METTL16 promotes hepatocellular carcinoma progression through downregulating RAB11B-AS1 in an m^{6}A-dependent manner. *Cell Mol Biol Lett*. 2022;27(1): 41.
88. Wang J, Tan L, Yu X, et al. lncRNA ZNRD1-AS1 promotes malignant lung cell proliferation, migration, and angiogenesis via the miR-942/TNS1 axis and is positively regulated by the m^{6}A reader YTHDC2. *Mol Cancer*. 2022;21(1):229.
89. Ni W, Yao S, Zhou Y, et al. Long noncoding RNA GAS5 inhibits progression of colorectal cancer by interacting with and triggering YAP phosphorylation and degradation and is negatively regulated by the m^{6}A reader YTHDF$_3$. *Mol Cancer*. 2019; 18(1):143.
90. Li G, Ma L, He S, et al. WTAP-mediated m^{6}A modification of lncRNA NORAD promotes intervertebral disc degeneration. *Nat Commun*. 2022;13(1):1469.
91. Pan J, Xie Y, Li H, et al. mmu-lncRNA 121686/hsa-lncRNA 520657 induced by METTL3 drive the progression of AKI by targeting miR-328-5p/HtrA3 signaling axis. *Mol Ther*. 2022; 30(12):3694—3713.
92. Wang X, Li Q, He S, et al. LncRNA FENDRR with m6A RNA methylation regulates hypoxia-induced pulmonary artery endothelial cell pyroptosis by mediating DRP1 DNA methylation. *Mol Med*. 2022;28(1):126.
93. Gu Y, Niu S, Wang Y, et al. *DMDRMR*-mediated regulation of m^{6}A-modified *CDK4* by m^{6}A reader IGF$_2$BP$_3$ drives ccRCC progression. *Cancer Res*. 2021;81(4):923—934.
94. Ye M, Dong S, Hou H, Zhang T, Shen M. Oncogenic role of long noncoding RNAMALAT1 in thyroid cancer progression through regulation of the miR-204/IGF$_2$BP$_2$/m6A-MYC signaling. *Mol Ther Nucleic Acids*. 2021;23:1—12.
95. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat Rev Mol Cell Biol*. 2020;21(8): 475—490.
96. Lu D, Thum T. RNA-based diagnostic and therapeutic strategies for cardiovascular disease. *Nat Rev Cardiol*. 2019;16(11): 661—674.
97. Li B, Li Y, Hu L, et al. Role of circular RNAs in the pathogenesis of cardiovascular disease. *J Cardiovasc Transl Res*. 2020; 13(4):572—583.
98. Yang Y, Fan X, Mao M, et al. Extensive translation of circular RNAs driven by N^6-methyladenosine. *Cell Res*. 2017;27(5): 626—641.
99. Di Timoteo G, Dattilo D, Centrón-Broco A, et al. Modulation of circRNA metabolism by m^{6}A modification. *Cell Rep*. 2020; 31(6):107641.
100. Chen YG, Chen R, Ahmad S, et al. *N*6-methyladenosine modification controls circular RNA immunity. *Mol Cell*. 2019; 76(1):96—109.e9.
101. Zhou C, Molinie B, Daneshvar K, et al. Genome-wide maps of m6A circRNAs identify widespread and cell-type-specific methylation patterns that are distinct from mRNAs. *Cell Rep*. 2017;20(9):2262—2276.

102. Wang Y, Wang Z. Efficient backsplicing produces translatable circular mRNAs. *RNA*. 2015;21(2):172—179.
103. Legnini I, Di Timoteo G, Rossi F, et al. Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis. *Mol Cell*. 2017;66(1):22—37.e9.
104. Wang L, Yu P, Wang J, et al. Downregulation of circ-ZNF609 promotes heart repair by modulating RNA N^6-methyladenosine-modified *Yap* expression. *Research*. 2022;2022:9825916.
105. Zhao J, Lee EE, Kim J, et al. Transforming activity of an oncoprotein-encoding circular RNA from human papillomavirus. *Nat Commun*. 2019;10(1):2300.
106. Leprivier G, Rotblat B, Khan D, Jan E, Sorensen PH. Stress-mediated translational control in cancer cells. *Biochim Biophys Acta*. 2015;1849(7):845—860.
107. Hansen TB, Wiklund ED, Bramsen JB, et al. miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA. *EMBO J*. 2011;30(21):4414—4422.
108. Liu CX, Li X, Nan F, et al. Structure and degradation of circular RNAs regulate PKR activation in innate immunity. *Cell*. 2019;177(4):865—880.e21.
109. Park OH, Ha H, Lee Y, et al. Endoribonucleolytic cleavage of m^6A-containing RNAs by RNase P/MRP complex. *Mol Cell*. 2019;74(3):494—507.e8.
110. Fischer JW, Busa VF, Shao Y, Leung AKL. Structure-mediated RNA decay by UPF_1 and G3BP1. *Mol Cell*. 2020;78(1):70—84.e6.
111. Fu Y, Zhuang X. m^6A-binding YTHDF proteins promote stress granule formation. *Nat Chem Biol*. 2020;16(9):955—963.
112. Haque S, Harries LW. Circular RNAs (circRNAs) in health and disease. *Genes (Basel)*. 2017;8(12):353.
113. Wang L, Xu GE, Spanos M, et al. Circular RNAs in cardiovascular diseases: regulation and therapeutic applications. *Research*. 2023;6:38.
114. Chen RX, Chen X, Xia LP, et al. N^6-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis. *Nat Commun*. 2019;10(1):4695.
115. Guo Y, Guo Y, Chen C, et al. Circ3823 contributes to growth, metastasis and angiogenesis of colorectal cancer: involvement of miR-30c-5p/TCF_7 axis. *Mol Cancer*. 2021;20(1):93.
116. Wu P, Fang X, Liu Y, et al. N6-methyladenosine modification of circCUX1 confers radioresistance of hypopharyngeal squamous cell carcinoma through caspase1 pathway. *Cell Death Dis*. 2021;12(4):298.
117. Xu J, Wan Z, Tang M, et al. N^6-methyladenosine-modified CircRNA-SORE sustains sorafenib resistance in hepatocellular carcinoma by regulating β-catenin signaling. *Mol Cancer*. 2020;19(1):163.
118. Du A, Li S, Zhou Y, et al. M6A-mediated upregulation of circMDK promotes tumorigenesis and acts as a nanotherapeutic target in hepatocellular carcinoma. *Mol Cancer*. 2022;21(1):109.
119. Liang L, Zhu Y, Li J, Zeng J, Wu L. ALKBH5-mediated m6A modification of circCCDC134 facilitates cervical cancer metastasis by enhancing HIF1A transcription. *J Exp Clin Cancer Res*. 2022;41(1):261.
120. Chen C, Yuan W, Zhou Q, et al. N6-methyladenosine-induced circ1662 promotes metastasis of colorectal cancer by accelerating YAP1 nuclear localization. *Theranostics*. 2021;11(9):4298—4315.
121. Xie F, Huang C, Liu F, et al. CircPTPRA blocks the recognition of RNA N^6-methyladenosine through interacting with IGF_2BP_1 to suppress bladder cancer progression. *Mol Cancer*. 2021;20(1):1—17.
122. Liu B, Liu N, Zhu X, et al. Circular RNA circZbtb20 maintains ILC3 homeostasis and function via Alkbh5-dependent m^6A demethylation of Nr4a1 mRNA. *Cell Mol Immunol*. 2021;18(6):1412—1424.
123. Yao B, Zhang Q, Yang Z, et al. CircEZH2/miR-133b/IGF_2BP_2 aggravates colorectal cancer progression via enhancing the stability of m^6A-modified CREB1 mRNA. *Mol Cancer*. 2022;21(1):140.
124. Ding L, Wang R, Zheng Q, et al. circPDE5A regulates prostate cancer metastasis via controlling WTAP-dependent N6-methyladenisine methylation of EIF_3C mRNA. *J Exp Clin Cancer Res*. 2022;41(1):187.
125. Huang R, Zhang Y, Bai Y, et al. N^6-methyladenosine modification of fatty acid amide hydrolase messenger RNA in circular RNA STAG1-regulated astrocyte dysfunction and depressive-like behaviors. *Biol Psychiatr*. 2020;88(5):392—404.
126. Zhang Z, Zhu H, Hu J. CircRAB11FIP1 promoted autophagy flux of ovarian cancer through DSC1 and miR-129. *Cell Death Dis*. 2021;12(2):219.
127. Jiang X, Xing L, Chen Y, et al. CircMEG3 inhibits telomerase activity by reducing Cbf5 in human liver cancer stem cells. *Mol Ther Nucleic Acids*. 2021;23:310—323.
128. Yu P, Wang J, Xu GE, et al. RNA m^6A-regulated *circ-ZNF609* suppression ameliorates doxorubicin-induced cardiotoxicity by upregulating FTO. *JACC (J Am Coll Cardiol)*. 2023;8(6):677—698.
129. Liu L, Gu M, Ma J, et al. CircGPR137B/miR-4739/FTO feedback loop suppresses tumorigenesis and metastasis of hepatocellular carcinoma. *Mol Cancer*. 2022;21(1):149.
130. Hogg SJ, Beavis PA, Dawson MA, Johnstone RW. Targeting the epigenetic regulation of antitumour immunity. *Nat Rev Drug Discov*. 2020;19(11):776—800.
131. Zhang Y, Rong D, Li B, Wang Y. Targeting epigenetic regulators with covalent small-molecule inhibitors. *J Med Chem*. 2021;64(12):7900—7925.
132. Chen B, Ye F, Yu L, et al. Development of cell-active N6-methyladenosine RNA demethylase FTO inhibitor. *J Am Chem Soc*. 2012;134(43):17963—17971.
133. Huang Y, Yan J, Li Q, et al. Meclofenamic acid selectively inhibits FTO demethylation of m6A over ALKBH5. *Nucleic Acids Res*. 2015;43(1):373—384.
134. Huang Y, Su R, Sheng Y, et al. Small-molecule targeting of oncogenic FTO demethylase in acute myeloid leukemia. *Cancer Cell*. 2019;35(4):677—691. e10.
135. Li F, Kennedy S, Hajian T, et al. A radioactivity-based assay for screening human m6A-RNA methyltransferase, METTL3-METTL14 complex, and demethylase ALKBH5. *J Biomol Screen*. 2016;21(3):290—297.
136. Moroz-Omori EV, Huang D, Kumar Bedi R, et al. METTL3 inhibitors for epitranscriptomic modulation of cellular processes. *ChemMedChem*. 2021;16(19):3035—3043.
137. Yankova E, Blackaby W, Albertella M, et al. Small-molecule inhibition of METTL3 as a strategy against myeloid leukaemia. *Nature*. 2021;593(7860):597—601.
138. Hong YG, Yang Z, Chen Y, et al. The RNA m6A reader $YTHDF_1$ is required for acute myeloid leukemia progression. *Cancer Res*. 2023;83(6):845—860.
139. Wilson C, Chen PJ, Miao Z, Liu DR. Programmable m^6A modification of cellular RNAs with a Cas13-directed methyltransferase. *Nat Biotechnol*. 2020;38(12):1431—1440.
140. Li X, Xiong X, Yi C. Epitranscriptome sequencing technologies: decoding RNA modifications. *Nat Methods*. 2016;14(1):23—31.
141. Garcia-Campos MA, Edelheit S, Toth U, et al. Deciphering the "m^6A code" via antibody-independent quantitative profiling. *Cell*. 2019;178(3):731—747.e16.
142. Wilson C, Chen PJ, Miao Z, Liu DR. Programmable m^6A modification of cellular RNAs with a Cas13-directed methyltransferase. *Nat Biotechnol*. 2020;38(12):1431—1440.
143. Sun X, Wang DO, Wang J. Targeted manipulation of m^6A RNA modification through CRISPR-Cas-based strategies. *Methods*. 2022;203:56—61.