Review

The crosstalk between m^6A RNA methylation and other epigenetic regulators: a novel perspective in epigenetic remodeling

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Abstract

Epigenetic regulation involves a range of sophisticated processes which contribute to heritable alterations in gene expression without altering DNA sequence. Regulatory events predominantly include DNA methylation, chromatin remodeling, histone modifications, non-coding RNAs (ncRNAs), and RNA modification. As the most prevalent RNA modification in eukaryotic cells, N^6-methyladenosine (m^6A) RNA methylation actively participates in the modulation of RNA metabolism. Notably, accumulating evidence has revealed complicated interrelations occurring between m^6A and other well-known epigenetic modifications. Their crosstalk conspicuously triggers epigenetic remodeling, further yielding profound impacts on a variety of physiological and pathological processes, especially tumorigenesis. Herein, we provide an up-to-date review of this emerging hot area of biological research, summarizing the interplay between m^6A RNA methylation and other epigenetic regulators, and highlighting their underlying functions in epigenetic reprogramming.

Key words: N^6-methyladenosine (m^6A); DNA methylation; chromatin remodeling; histone modification; non-coding RNA (ncRNA); RNA modification

Introduction

Epigenetics, which represents the modulation of heritable phenotypes without any alterations in DNA sequences, has become a significant regulatory mechanism of diverse physiological or pathological processes. The scope of epigenetics is extensive, typically including DNA methylation, chromatin remodeling, histone modification, non-coding RNAs (ncRNAs) and RNA modification [1]. The first three members are superstars in epigenetics, and have been studied extensively so far. ncRNAs, mainly comprised of microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) [2], have provoked accumulating interests nowadays. In addition, there are more than 100 categories of RNA chemical modifications, and the common types include N^6-methyladenosine (m^6A), pseudouridine (ψ), 2'-O-methylation (Nm), m^1A, 5-methylcytosine (m^5C), adenosine-to-inosine (A-to-I), and N^6, 2'-O-dimethyladenosine (m^6Am) [3-7]. Notably, m^6A RNA methylation is the most abundant internal mRNA modification in mammals [8]. With the rapid development of detection methodologies and high-throughput sequencing, the genome-wide features of m^6A are being uncovered, which have increasingly attracted the attention of bioscience researchers.

In the case of total RNA, m^6A methylation occurs in approximately 0.1-0.4% of adenosines [9], predominantly located at 3’ untranslated regions (3’UTRs), near stop codons and within the long internal exon [10, 11]. DRACH sequences are verified as the consensus motif of m^6A (D = G/A/U; R = G/A; H = U/A/C) [12]. Strikingly, m^6A modification is a reversible and dynamic process, which is deposited
by methyltransferases (also called “writers”), and removed by demethylases (also called “erasers”) (Figure 1) [13, 14]. Subsequently, m^6^A-binding proteins (also called “readers” or “effectors”) recognize and bind to the m^6^A marks of targeted RNAs to influence their RNA metabolism, including stability, translation, alternative splicing and transport [15-18]. Furthermore, m^6^A plays a key role in far-ranging biological processes, such as cell differentiation, tissue development, environmental stress response, spermatogenesis, immune homeostasis and tumorigenesis [13].

Remarkably, it is commonly acknowledged that epigenetic regulations are intricate due to the interactions among epigenetic modifiers [19, 20]. As a research frontier, m^6^A is just like a storm center to frequently interact with its peripheral partners, the other epigenetic modulators. These partners can be modified and regulated by m^6^A modification, while m^6^A methylation may also be efficiently controlled by these regulators [20-22]. The coordinated relationships between m^6^A machinery and any other epigenetic counterparts elicit the epigenetic remodeling, which accounts for the perplexing modulations of various bioprocesses. Herein, we summarize the up-to-date findings about the interplay of m^6^A RNA methylation and other epigenetic modifications (Tables 1-3), and demonstrate how these associations impact biological functions, particularly in oncogenesis and tumor progression, highlighting the potential of m^6^A as a therapeutic target in the clinical practice.

### The genealogy of m^6^A modification

**m^6^A writers**

The installation of m^6^A methylation is manipulated by the methyltransferase complex (MTC), which largely comprises of methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and Wilms tumor 1-associated protein (WTAP) [23]. METTL3 functions as a key catalytic element to facilitate the formation of m^6^A, while METTL14 acts as an RNA-binding scaffold to promote the enzymatic activity of METTL3 [24, 25]. WTAP is responsible for the stabilization of the METTL3-METTL14 heterodimer and ensuring their accurate localization to nuclear speckles [26]. Moreover, there are other co-factors involved in the conformation of MTC, including vir-like m^6^A methyltransferase associated (VIRMA, also known as KIAA1429) [27], Cbl proto-oncogene like 1 (CBLL1, also known as HAKAI), RNA-binding motif protein 15 (RBM15) with its parologue RBM15B [28], and zinc finger CCCH domain-containing protein 13 (ZC3H13) [29, 30]. Notably, METTL16 is another m^6^A methyltransferase, which dominates cellular SAM levels and mediates m^6^A modification of U6 small nuclear RNAs (snRNAs), pre-mRNAs or certain types of lncRNAs [31, 32]. Additionally, METTL5 and ZCCHC4 have been identified as m^6^A methyltransferases for 18S rRNA and 28S rRNA, respectively [33, 34].

### Table 1. The complicated interactions between m^6^A and other epigenetic modifications

| Categories of epigenetics | Related component | m^6^A regulators | Mechanisms | Reference(s) |
|---------------------------|-------------------|------------------|------------|--------------|
| DNA methylation           |                   |                  |            |              |
| DNA methyltransferase     | SIDML2            | SIALKBH2         | SIDML2-induced DNA methylation regulates the m^6^A demethylation SIALKBH2, while SIALKBH2-guided m^6^A demethylation strengthens the stability of 5mC demethylase SIDML2 in turn. | [62] |
| DNMT1, DNMT3a             | METTL3            |                  | The binding of DNMT1 and DNMT3a to METTL3 promoter is reduced by cigarette smoke condensate (CSC), leading to the hypo-methylation of METTL3 and facilitating its expression. | [64] |
| /                          | ALKBH5            |                  | The CpG island of ALKBH5 is hypomethylated by CSC, which increases ALKBH5 expression. | [65] |
| Chromatin remodeling      | BAF155            | RBM15            | RBM15 accelerates the decay of chromatin remodeling factor BAF155 via the m^6^A methylation machinery. | [67] |
| carRNAs                   | METTL3            | YTHDC1           | METT3L promotes m^6^A methylation of chromosome-associated regulatory RNAs (carRNAs), while YTHDC1 mediates their degradation. | [22] |
| Histone modification      | H3K27ac           | METTL14          | METTL14 not only alters H3K27me3 modification, but also regulates H3K27ac modification by destabilizing CBP and p300 RNAs. | [21] |
| H3K27me3, CBP, p300        | METTL3            | Ezh2             | METT3L deposits m^6^A modification on histone methyltransferase Ezh2, which increases the level of H3K27me3. | [70] |
| H3K4me3                   | METTL3, METTL14, WTAP |                  | The m^6^A modification catalyzed by METT3L/METTL14/WTAP complex substantially strengthens H3K4me3 modification. | [71] |
| JMJD6                     | hnRNP A2B1        |                  | Arginine demethylase JMJD6 activates hnRNP A2B1 through facilitating its demethylation at Arg^22^, which accelerates the decay of METTL3 triggers its transcription. | [72] |
| H3K27ac                   | METTL3            |                  | H3K27ac modification on the promoter of METTL3 triggers its transcription. | [73] |
| H3K4me3, KDM5C            | METTL14          |                  | KDM5C-mediated demethylation of H3K4me3 suppresses METTL14 transcription. | [74] |
| H3K36me3                   | METTL14          |                  | H3K36me3 mark recognized by METTL14 promotes the binding of m^6^A methyltransferase complex to adjacent RNA polymerase II, depositing m^6^A co-translationally. | [75] |
m^6_A erasers

Fat mass and obesity-associated (FTO) and alkB homolog 5 (ALKBH5) are the only two known m^6_A demethylases to date. Although both demethylases belong to the AlkB family of dioxygenases, they eliminate m^6_A through different mechanisms. As the first identified m^6_A demethylase, FTO induces demethylation activity depending on the oxidative function, which requires iron (II) and α-KG [35]. Specifically, FTO initially oxidizes m^6_A to form intermediate products, including N^6-hydroxymethyladenosine (hm^6_A) and N^6-formyladenosine (f^6_A), and subsequently hydrolyzes the products into adenosine, which is a sequential and multi-step procedure. However, the catalytic process mediated by ALKBH5 is a one-step reaction process, in which ALKBH5 directly abrogates m^6_A in an oxidative-dependent manner [36]. Furthermore, a discrepancy has been observed in the recognition of substrates between ALKBH5 and FTO. ALKBH5 acts as an m^6_A-specific demethylase, while FTO can demethylate a variety of RNA modifications, such as m^6_A, m^6_Am and m^1_A [37].

### Table 2. The specific molecular mechanisms and biological functions of m^6_A modification on ncRNAs

| m^6_A-related enzymes | Non-coding RNAs | Mechanisms | Biological functions | Reference |
|-----------------------|----------------|------------|---------------------|-----------|
| METTL3, METTL14       | miR-221/222    | Promoting miR-221/222 maturation. | Accelerating cell proliferation | [110] |
| METTL3                | miR-1246       | Facilitating miR-1246 maturation. | Promoting the metastasis of colorectal cancer. | [111] |
| METTL3, WTAP, ALKBH5  | miR-873-5p     | Strengthening miR-873-5p maturation. | Blocking oxidative stress and apoptosis in colostrin-evoked nephrotoxic y. | [112] |
| METTL3                | miR-143-3p     | Enhancing miR-143-3p maturation. | Facilitating angiogenesis and brain metastasis of lung cancer. | [113] |
| METTL3, NKAP          | miR-25-3p      | Accelerating miR-25-3p maturation. | Driving osteogenic differentiation of bone marrow-deriv ed mesenchymal stem cells. | [114] |
| METTL3, YTHDF3        | miR-7212-5p    | Mediating miR-7212-5p maturation. | Inhibiting osteoblast differentiation and fracture healing. | [115] |
| METTL3                | miR-126        | Inducing miR-126 maturation. | Promoting the progression of pancreatic cancer. | [66] |
| METTL3, MALAT1        | Enhancing the stability of MALAT1. | Inducing drug resistance and metastasis of non-small cell lung cancer. | [128] |
| WTAP, XIST            | Co-localizing with XIST. | Participating in XIST-mEDIATE silencing. | | [130] |
| METTL3, WTAP, RBM15/ 158, YTHDF1, METTL14, YTHDF2 | XIST | Promoting XIST-mediated transcriptional repression. | | [28] |

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2 mRNA-binding proteins (IGF2BP1/2/3) [40], and heterogeneous nuclear ribonucleoprotein (HNRNP) family (HNRNP2B1, HNRNPC and HNRNPG) [41-43], which exert a great influence on the destiny of targeted RNAs.

**Table 3.** The underlying molecular mechanisms and biological functions of ncRNAs on m6A modification

| Categories | Non-coding RNAs | m6A-related enzymes | Mechanisms | Biological functions | References |
|------------|-----------------|----------------------|------------|----------------------|------------|
| METTL3     | LINC00958       | YTHDF2               | Inhibiting the expression of YTHDF2 | /            | [121]       |
| METTL3,   | LINCAROD       | METTL3               | Suppressing the growth and metastasis of hepatoblastoma |               | [122]       |
| METTL14    | ALKBH5, YTHDF2 | METTL3               | Attenuating the expression of METTL3. |               | [123]       |
| VIRMA      | CCA1/2          | YTHDF2               | Maintaining the stability of IGF2BP2. |               | [134]       |
| IGF2BP2    | DANCER          | E2F4                 | Recruiting METTL3 to methylate and stabilize ARHGAP5. |               | [145]       |
| ALKBH5, YTHDF2 | PVT1         | YTHDF2               | Recruiting METTL3 to methylate and stabilize ARHGAP5. |               | [146]       |
| METTL3     | RHPN1-AS1       | METTL3               | Recruiting METTL3 to methylate and stabilize ARHGAP5. |               | [147]       |
| METTL3,   | LINC000278      | GNAS                 | Interacting with ALKBH5 to demethylate and stabilize GNAS. |               | [148]       |
| METTL3,   | LINC000278      | FOXM1-AS1            | Increasing the binding of ALKBH5 to FOXM1 pre-mRNA. |               | [149]       |
| METTL3,   | LINC000278      | KIAA1429             | Enhancing the interaction between KIAA1429 and GATA3 pre-mRNA. |               | [150]       |
| METTL3,   | LINC000266-1    | IGF2BP1              | Promoting the recognition of IGF2BP1 upon m6A-modified RNAs like c-Myc. |               | [151]       |
| YTHDF3     | GAS5            | METTL3               | Attenuating the expression of METTL3. |               | [152]       |
| METTL3,   | LINC000266-1    | GATA3-AS             | Accelerating the translation of GATA3 pre-mRNA. |               | [153]       |
| METTL3,   | LINC000266-1    | circRNAG1            | Capturing ALKBH5 and reducing its intranuclear translation. |               | [154]       |
| YTHDF3     | GAS5            | METTL3               | Accelerating the translation of GATA3 pre-mRNA. |               | [155]       |
| m6A-circRNA | YTHDC1          | circRNA-m6A          | Attenuating the expression of circRNA-m6A. |               | [156]       |

**m6A readers**

The m6A readers primarily consist of YT521-B homology (YTH) domain family proteins (YTHDF1/2/3), YTH domain containing proteins (YTHDC1/2) [15-17, 38, 39], insulin-like growth factor...
the conventional views and reveals that there is no evidence to demonstrate the direct role of YTHDF proteins in promoting RNA translation [45]. They also put forward an unified model of m⁶A function in which m⁶A modification predominantly affects mRNA degradation through the combined action of three redundant YTHDF proteins. These controversial viewpoints show the complex roles of YTHDFs in the m⁶A-based regulation, which require further discussion and verification. YTHDC1 is an m⁶A reader which not only regulates alternative splicing and nuclear export, but also accelerates mRNA degradation [17, 18, 22]. YTHDC2 can induce the translation elongation of m⁶A-modified mRNAs, but also reduce the stability of certain targeted mRNAs [39, 46, 47]. Furthermore, IGF2BP3s are another cluster of readers whose K homology (KH) domains are required for m⁶A recognition. Generally, IGF2BPs can enhance the stability and translation of m⁶A-containing mRNAs [40, 48-52].

The binding of HNRNPA2B1 and m⁶A is mediated by a mechanism called “m⁶A switch”, in which alteration in the structure of targeted RNA caused by m⁶A methylation enhances the combination of m⁶A and HNRNPA2B1 [41, 43]. HNRNPA2B1 not only recognizes nuclear m⁶A-bearing transcripts to promote alternative splicing, but also strengthens primary miRNA processing [53]. HNRNPG is capable of regulating alternative splicing or gene expression [42]. Furthermore, HNRNPC may participate in the RNA processing of mRNAs or IncRNAs depending on m⁶A modification [41].

Strikingly, some reader-like effectors are also crucial for m⁶A regulation. For example, eIF3 can facilitate m⁶A-mediated translation [54]. METTL3 has the capacity to promote translation of several mRNAs independent of its methyltransferase activity and other m⁶A-binding proteins [55]. In addition, HuR is recognized to be involved in m⁶A-related events [56]. However, the regulatory modes of HuR are currently controversial.

**The interplay between m⁶A and other epigenetic modifications**

**m⁶A and DNA methylation**

DNA methylation is a well-known and crucial epigenetic modification [57]. Studies have revealed that DNA 5mC and 6mA methylations are the most common types of DNA modifications in eukaryotes and prokaryotes, respectively. Specifically, 5mC is generated by DNA methyltransferase 3A (DNMT3A) and DNMT3B [58], while demethylated either actively via ten-eleven translocation (TET) or passively by diluting DNA methylation labels during DNA replication [59, 60]. In addition, N6AMT1 and ALKBH1 have been characterized as methyltransferase and demethylase of 6mA modification, respectively [61].

Notably, an RNA methylome manifests the crosstalk between RNA and DNA methylation in fruit ripening [62]. The m⁶A demethylase SIALKBH2, which is responsible for the decreased m⁶A levels of fruit-ripening genes, is modulated by SIDML2-contained DNA methylation. In turn, the stability of 5mC demethylase SIDML2 is strengthened by SIALKBH2-guided m⁶A demethylation (Figure 2A). Most recently, a comprehensive interplay between 5mC and m⁶A regulators across 33 cancer species based on bioinformatics analyses has been reported [63]. The two types of methylations are functionally correlated with significant co-occurrences of genetic mutations. Some of the pivotal m⁶A/5mC genes are combined to establish an epigenetic module eigengene (EME). Interestingly, an elevated EME implies a strongly proliferative and aggressive cellular status, low inflammatory and immune infiltration, and enhanced enrichment of stromal signatures. Furthermore, EME level is useful to predict prognosis of cancer patients.

![Figure 1. The dynamic and reversible processes of m⁶A modification. “Writers” deposit m⁶A methylation on RNAs, while “erasers” remove the m⁶A marks. Then “readers” are responsible for regulating the fate of targeted RNAs.](http://www.thno.org)
In pancreatic cancer, cigarette smoke condensate (CSC) is able to induce the hypomethylation of METTL3 through attenuating the bindings of DNMT1 and DNMT3a to the METTL3 promoter, which leads to the up-regulation of METTL3 and the following increased m6A levels of pri-miR-25 (Figure 2B) [64]. However, CSC can also contribute to a diminished m6A abundance through triggering the hypomethylation of ALKBH5 CpG island in esophageal squamous cell carcinoma [65]. Thus CSC seems to be a powerful factor to indirectly influence m6A modification via the straightforward impact on DNA methylation. Moreover, m6A profiling based on human fetal tissues reveals a preferential occupation of m6A on CpG-rich promoters. CpG-related promoters are capable of modulating m6A levels [66]. These results may suggest the co-transcriptional process of m6A biogenesis and DNA methylation.

m6A and chromatin remodeling

Chromatin remodeling is the rearrangement of chromatin state. An open or condensed state determines the accessible or unapproachable access for DNA binding proteins. Nowadays, several studies have demonstrated the crosstalk between chromatin remodeling and m6A modification. BAF155 is a chromatin remodeling factor. RBM15 can negatively regulate the expression of BAF155 mRNA by decreasing its stability and promote its decay in an m6A-dependent manner [67]. Notably, the regulation capacity of RBM15 on BAF155 requires the activity of METTL3. Furthermore, a reverse correlation between METTL3/YTHDC1 and chromatin accessibility in mouse embryonic stem cells (ESCs) is observed [22]. Specifically, METTL3 promotes the m6A methylation of chromosome-associated regulatory RNAs (carRNAs), while YTHDC1 participates in the degradation of these m6A-marked RNAs. Thus METTL3/YTHDC1-guided m6A modification regulates the chromatin state and subsequent transcription by governing the expression of carRNAs (Figure 2C).

Remarkably, a study has revealed the deposition of m6A in chromatin-associated nascent pre-mRNAs from Hela cells. This m6A methylation, which is mainly present in exons and rarely in introns, is
accomplished when mRNA is released into nucleoplasm. Surprisingly, m6A modification is required for the cytoplasmic mRNA stability of nascent transcripts, but not for the majority of splicing events [68].

m6A and histone modification

Histone modification is a significant participant of post-translational regulations, which is involved in chromatin structure modulation, nucleosome dynamics and gene transcription. It primarily contains histone methylation, acetylation and ubiquitination. Interestingly, some modifications lead to the repression of transcription like H3K9me2/3 and H3K27me3, while others are associated with the activation of transcription including H3K4me1-3, H3K27me1, H3K36me1-3 and H3K27ac [69].

During cell development, METTL14 plays a vital role in the proliferation and differentiation of neural stem cells (NSCs). Surprisingly, the increased levels of H3K27ac, H3K4me3 and H3K27me3 modifications are observed when METTL14 is deleted. MTT assays demonstrate that m6A modulates the proliferation of NSCs partially via regulating H3K27ac and H3K27me3. Mechanistically, METTL14-mediated m6A methylation suppresses the stability of both CREB binding protein (CBP) and p300 transcripts which are the crucial modifiers of H3K27ac (Figure 2D) [21]. In addition, METTL3-mediated m6A modification is necessary for neuronal development and neurogenesis. METTL3 regulates the m6A-modified histone methyltransferase Ezh2, which further advances the level of H3K27me3 (Figure 2E) [70]. For erythropoiesis, m6A enzymes facilitate the translation of erythroid genes, especially those encoding SETD histone methyltransferases. The impairment of m6A leads to a substantial inhibition of H3K4me3 modification which is responsible for KLF1-centered transcriptional program required for erythropoiesis, heme synthesis or hemoglobin assembly [71]. These studies suggest the divergent impacts on histone methylation induced by m6A, which may indicate that m6A-mediated histone regulation is cell-type-specific.

Apart from m6A-modulated histone modifications, histone modifiers also intimately participate in m6A rearrangement. The m6A reader hnRNPA2B1 is implicated in the immune response to DNA viruses. Herpes simplex virus-1 (HSV-1) infection induces the dimerization of hnRNPA2B1, which guides its nucleo-cytoplasmic translocation. Simultaneously, the arginine demethylase JMJD6 promotes the demethylation of hnRNPA2B1 at Arg226 and activates its translocation to cytoplasm, which further magnifies the expression of IFN-β (Figure 2E) [72]. In gastric cancer, the promoter of METTL3 is marked by p300-regulated H3K27ac modification, which triggers the transcription of METTL3 and then leads to an elevated m6A level of HDGF (Figure 2F) [73]. Furthermore, KDM5C-guided demethylation of H3K4me3 modification suppresses the transcription of METTL14 which can restrain the metastasis of colorectal cancer (CRC) via promoting the m6A level of SOX4 mRNA [74].

Moreover, two studies have afforded systematic evidence for the precise and dynamical deposition of m6A and histone modification. Huang et al. find that m6A peaks associated with H3K36me3 marks mainly locate near stop codons, while those H3K36me3 loci not modified by m6A are enriched in the coding sequence (CDS) or intron [75]. The correlated positions imply their intertwined relationships. Intriguingly, although H3K36me3 cannot impact the expression of m6A key enzymes, it may affect the interaction between m6A enzymes and their targets. In other words, H3K36me3 is able to recruit m6A complex to deposit m6A imprinting. The fundamental element for the binding of m6A complex and H3K36me3 is METTL14 which is further identified to recognize H3K36me3 marks via a Pol II-independent pattern during transcription elongation [75]. Additionally, Li et al. clarify that METTL3/METTL14-mediated m6A methylation modulates the levels of H3K9me2 [76]. The genome-wide correlation between m6A and KDM3B (H3K9me2 demethylase) is identified. To be specific, YTHDC1 recruits KDM3B to m6A-marked chromatin regions, triggering H3K9me2 demethylation and subsequent activation of gene expression. Conservatively, the co-occurrence of H3K36me2 and m6A is found in plants as well [77]. All these investigations reveal the co-transcriptional interplay or even co-occupancy between m6A and histone modification.

m6A and other RNA modifications

m6A and m1A

Currently, m1A is considered as a reversible modification in tRNAs, rRNAs, and mRNAs, which is methylated and demethylated by TRMTs and ALKBH1/3, respectively [78, 79]. Remarkably, increasing evidence indicates a close link between m1A and m6A. Wei et al. discover that FTO has the ability to mediate both nuclear and cytoplasmic demethylation of m1A in tRNAs, and to subsequently suppress the RNA translation process [37]. The special structure of FTO is analogous to the tRNA m5C methyltransferase NSUN6, which explains why another m6A demethylase ALKBH5 cannot recognize m1A at tRNAs as a substrate.
The m^6^A-binding proteins YTHDF1-3 and YTHDC1 are capable of directly binding to m^1^A sites. YTHDF2 accomplishes the recognition of m^6^A and m^A depending on its conserved residue Trp432 [80]. Functionally, YTHDF2 facilitates the degradation of m^1^A-modified transcripts [81].

Fortunately, two approaches including DART-seq and m^A-IP-seq/m^A-Aquant-seq, have been used to achieve genome-wide mapping of m^6^A and m^A with a single-base resolution, respectively [82, 83]. However, further research should be conducted to explore the mechanisms between the two types of modifications via using the novel tools.

m^6^A and m^3^C

The m^3^C modification, which is the methylation of cytosine at carbon 5, is catalyzed by NSUN proteins and DNMT2 [84, 85], and primarily occurs in tRNAs, rRNAs, and mRNAs [86]. Previous studies have reported that m^3^C methylation is of great significance in the RNA stability, export and transcription [87].

Remarkably, there is a subtle relationship between m^3^C and m^6^A modifications. Courtney et al. demonstrate that murine leukemia virus (MLV) transcripts exhibit high levels of m^6^A and m^3^C modifications, which lead to a high level of viral replication. Mechanistically, the ectopic expression of YTHDF2 facilitates MLV replication, while the inhibition of m^6^C writer NSUN2 hinders MLV replication [88], which suggests that m^6^A may cooperate with m^3^C to engage in some biological events. Coincidently, a direct synergistic effect of m^6^A and m^3^C has been reported [89]. METTL3/METTL14-catalyzed m^6^A methylation and NSUN2-induced m^3^C methylation can jointly enhance the expression of p21 mRNA in response to oxidative stress-triggered cellular senescence in tumor cells (Figure 2G). In addition to the cooperative relationship, an interaction between m^6^A and m^3^C has been observed. Specifically, METTL3/METTL14-mediated m^6^A modification can promote NSUN2-mediated m^3^C modification, and vice versa.

In addition, m^6^A reader YTHDF2 is capable of recognizing and binding to m^3^C in RNA [90]. Deletion of YTHDF2 results in a remarkably expanded m^3^C level in rRNA. Interestingly, YTHDF2 participates in the regulation of pre-rRNA processing, which may be achieved via its modulation of m^3^C level.

m^6^A and A-to-I

The transition of A-to-I is processed by adenosine deaminases acting on RNA (ADAR) enzymes, which is a principal form of RNA editing [91]. It is reported that A-to-I is a key factor influencing RNA metabolism, such as miRNA processing [92].

A reverse correlation between m^6^A and A-to-I has been identified using genomic analyses (Figure 2H). Loss of m^6^A modification contributes to the elevated level of A-to-I editing via a favorable association of ADAR with m^6^A-depleted transcripts. However, the underlying mechanism has not been fully elucidated. One possible reason for the occurrence is that the alteration of m^6^A-induced RNA structure may mediate the binding of ADAR and targeted genes. The occupation of m^6^A enzymes on RNAs may interfere with the localization of ADAR [4]. However, whether A-to-I is capable of modulating m^6^A level remains indeterminate.

m^6^A and pseudogene

Pseudogene is a type of genomic element, which is partially homologous to corresponding functional genes, although lacks protein-coding capability due to mutations. Pseudogene widely participates in gene regulation [93].

Studies have revealed that there is a potential association between m^6^A and pseudogenes. Olfr29-ps1 is a lncRNA pseudogene, which is stimulated by cytokine IL-6 in myeloid-derived suppressor cells (MDSCs). METTL3-mediated m^6^A methylation facilitates the expression of Olfr29-ps1, and simultaneously enhances its sponge to miR-214-3p (Figure 2I). Then MyD88, which is suppressed by miR-214-3p, is up-regulated to amplify the differentiation and immunosuppressive effects of MDSCs [94]. Moreover, it is reported that m^6^A and pseudouridine (ψ) can collaboratively disrupt the binding of hPUM2 to its targeted RNAs [95].

In addition, m^6^A and ψ play a crucial role in immunity. Durbin et al. apply a well-accepted RIG-I-related platform to examine the immunosuppressive potential of various RNA modifications [96]. The results reveal that either m^6^A or ψ negatively correlates with the alleviated innate immune signaling. Specifically, m^6^A-modified RNAs may poorly bind to RIG-I. Although ψ-containing RNAs can intimately interact with RIG-I, they are unable to initiate the canonical RIG-I antiviral signaling.

m^6^A and m^6^Am

When the transcription initiation nucleoside of mRNA is 2-O-methyladenosine (Am), m^6^Am methyltransferase PCIF1 is capable of catalyzing methylation on its N^6^ position to further generate m^6^Am, which is dependent on the structure of 7-methylguanosine (m^7^G) cap [97-101]. Studies have revealed that m^6^Am can reinforce the stability of transcripts [102], while the findings about its effects on translation are inconsistently identified. Akichika
et al. illustrate that m\textsuperscript{6}Am enhances the translation of capped mRNAs [97]. However, another study suggests that m\textsuperscript{6}Am may impede cap-dependent translation [98].

Several studies demonstrating the genome-wide landscape of m\textsuperscript{6}A and m\textsuperscript{6}Am have been conducted, which provide reliable evidence for their relationship [103-105]. The conserved m\textsuperscript{6}Am signals can be detected in WTAP and ALKBH5, while the non-conserved m\textsuperscript{6}Am signals can be identified in METTL3. Additionally, the non-conserved m\textsuperscript{6}A signals can be found in PCIF1 [105]. Furthermore, FTO has been demonstrated to target m\textsuperscript{6}Am. Functionally, FTO is responsible for the demethylation of m\textsuperscript{6}Am in snRNA [37]. Nevertheless, additional functional relevance of m\textsuperscript{6}A and m\textsuperscript{6}Am remains to be explored.

m\textsuperscript{6}A and ncRNAs

m\textsuperscript{6}A modification exists in almost all types of ncRNAs, especially in miRNAs, IncRNAs and circRNAs. They are all vigorous performers participating in extensive biological processes, particularly in tumor malignancy. The crosstalk of m\textsuperscript{6}A and ncRNAs is pervasive and inspiring, extending the scope of epigenetics.

m\textsuperscript{6}A-miRNA

miRNA is a short non-coding RNA (no more than 22 nucleotides), and links to a variety of biological processes such as tumor growth, drug resistance, cell differentiation, and cellular senescence [106]. Initially, primary miRNA (pri-miRNA) is cleaved into precursor miRNA (pre-miRNA) by the microprocessor complex comprising of endonuclease Drosha and DGCR8 protein. After being transported to cytoplasm by exportin 5, pre-miRNA is further cleaved by Dicer to release the double-strands RNAs, which are then loaded onto an AGO protein constituting the RNA-induced silencing complex (RISC) [107].

Intriguingly, m\textsuperscript{6}A is the mark for advancing the processing of pri-miRNAs [108]. METTL3 is sufficient to methylate massive pri-miRNAs to reinforce miRNA maturation through recruiting DGCR8 and m\textsuperscript{6}A reader HNRNPA2B1 (Figure 3A). Moreover, HNRNPA2B1 interacts with DGCR8 to promote its binding to pri-miRNAs, which enhances the continuous generation of pri-miRNAs [53, 108]. There are plenty of illustrations about this regulatory pattern. In bladder cancer, METTL3 accelerates cell proliferation by promoting the maturation of pri-miR221/222 which targets at PTEN [109]. In CRC, METTL3 accounts for the aberrant m\textsuperscript{6}A modification and boosts the production of mature miR-1246, which suppresses the SPRED/MAPK signaling [110]. Wang et al. clarify that up-regulation of METTL3 blocks oxidative stress and apoptosis in colistin-evoked

Figure 3. The functions and mechanisms of m\textsuperscript{6}A modification on ncRNAs. (A) m\textsuperscript{6}A promotes the maturation of miRNA. (B) m\textsuperscript{6}A modulates IncRNA level. (C) m\textsuperscript{6}A facilitates IncRNA to combine with miRNA. (D) m\textsuperscript{6}A interferes the binding of IncRNA to proteins. (E) m\textsuperscript{6}A mediates the cytoplasmic export of circRNA. (F) m\textsuperscript{6}A regulates circRNA translation. (G) m\textsuperscript{6}A assists the innate immune system to recognize self circRNA.
nephrotoxicity via the promotion of miR-873-5p mature process and the regulation of Keap1-Nrf2 pathway [111]. Besides, mimicking the function of Dicer, METTL3-mediated m^6^A methylation leads to the splicing of pre-miR-143-3p which impairs VASH1 expression to facilitate angiogenesis and metastasis of lung cancers [112]. Moreover, METTL3 increases the m^6^A modification of pre-miR-320 and drives osteogenic differentiation of bone marrow-derived mesenchymal stem cells [113]. Another study demonstrates that the maturation of miR-7212-5p is impelled by METTL3-mediated m^6^A modification, while the miR-7212-5p/FGFR3 axis accounts for the regulation of osteoblast differentiation and fracture healing [114]. In addition, an interesting study shows that CSC activates the excessive miR-25-3p maturation dependent on m^6^A mechanism in only the m^6^A reader but also a splicing factor to demonstrate that the maturation of miR-7212-5p is driven by METTL3-mediated m^6^A modification, while the miR-7212-5p/FGFR3 axis accounts for the regulation of osteoblast differentiation and fracture healing [114]. In addition, an interesting study shows that CSC activates the excessive miR-25-3p maturation dependent on m^6^A mechanism in pancreatic cancer [64]. The enhancement of METTL3 triggered by CSC contributes to the up-regulation of m^6^A level on pri-miR-25. Then NKAP serves as not only the m^6^A reader but also a splicing factor to stimulate the processing of pri-miR-25. Accumulating miR-25-3p suppresses PHLPP2, leading to the activation of AKT-p70S6K signaling [64]. Except for METTL3, another m^6^A writer METTL14 also modulates the maturation of miRNAs analogously. As a suppressor in hepatocellular carcinoma (HCC), METTL14 interacts with DGCR8 to promote the processing of pri-miR-126 via an m^6^A-dependent pattern, triggering the enhanced level of miR-126 which represses the tumor metastasis [115].

Now that m^6^A is frequently enriched in 3' UTRs (near stop codons), and miRNA binding sites on mRNA are also commonly observed within 3' UTRs, the relationship between m^6^A and miRNA binding is discussed. However, an inverse localization pattern is identified [10]. One reasonable explanation is that moderate spatial distance may be beneficial for mutual effects between m^6^A and miRNA. Actually, deficiency of m^6^A caused by loss of METTL3 or METTL14 restrains the miRNA-mRNA interaction as well as boosts HuR-mRNA interaction, which finally stabilizes the corresponding transcript [116]. A more vivid example is provided by Zhang et al. [117]. The m^6^A residue is found in the 3’ UTR of YAP (353-357), and this modification is crucial for the conjugation of miR-582-3p and YAP. Hence, m^6^A modification may trigger the binding of miRNAs and targeted genes.

Additionally, AGO2 mRNA is highly methylated and positively modulated by m^6^A methyltransferases in human diploid fibroblasts. The miRNA abundance is controlled by m^6^A level based on the stability of AGO2 [118]. Knuckles et al. propose a model to delineate the RNA fate determined by m^6^A and microprocessor [119]. In normal temperature, METTL3-centered complex deposits the m^6^A labels to massive RNAs containing m^6^A, pri-miRNAs, lncRNAs and snoRNAs, followed by the induction of their degradation mediated by DGCR8. However, acute heat stress leads to the re-localization of the m^6^A complex and DGCR8 at heat-shock genes to facilitate their decay. Meanwhile, those transcripts previously modulated by METTL3 and DGCR8 accumulate. This is an indirect fashion of m^6^A to control the degradation of miRNAs or other ncRNAs.

**miRNA-m^6^A**

A bidirectional relationship exists between miRNAs and m^6^A because miRNAs can regulate m^6^A-related events as well. Dicer, but not AGO protein, mediates the formation of m^6^A without altering the amount of methyltransferases or demethylases, and it may modulate nuclear speckle localization of METTL3 [120]. miRNAs are able to trigger de novo m^6^A methylation through a sequence pairing pattern. Moreover, miRNAs are responsible for the manipulation of the binding of METTL3 to miRNA site-containing mRNAs to affect m^6^A abundance, which is tightly associated with cell reprogramming to pluripotency [120]. In HCC, miR-145 governs m^6^A level by inhibiting the expression of YTHDF2 [121]. METTL3 is targeted by miR-186, and it activates Wnt/β-catenin signaling in hepatoblastoma [122]. miRNA let-7g which is inhibited by HBXIP, attenuates the expression of METTL3. Simultaneously, HBXIP is activated by METTL3 in an m^6^A-dependent manner [123]. The positive feedback loop elaborates the complicated connection between miRNA and m^6^A.

**m^6^A-lncRNA**

LncRNAs are a group of non-coding transcripts longer than 200 nucleotides. The functions of lncRNAs are diverse, including regulating chromatin topology, serving as scaffolding for proteins or RNAs, governing RNA stabilization and transcription, or even producing peptides [124]. LncRNAs can be modulated via multiple levels containing transcriptional regulation, post-transcriptional processing and degradation control [125]. Importantly, the interaction between lncRNAs and m^6^A modification is a novel annotation (Figure 3B-D). Xiao et al. have generated the whole-transcriptome m^6^A landscape of human fetal tissues. Numerous lncRNAs are methylated by m^6^A especially in kidney, placenta and brain. Enhancer lncRNAs (originated from enhancers) have a higher enrichment in m^6^A modification compared with other lncRNAs. The distribution of m^6^A on lncRNAs is nearly balanced among 5’ UTR, CDS and 3’ UTR, which is different.
from the distribution on mRNA. Meanwhile, the proportion of m6A methylation on lncRNAs is lower than on mRNAs [66].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a highly conserved nuclear lncRNA which is closely related to the metastasis of tumors [126]. As an abundant and essential transcript, MALAT1 is a paradigm to describe m6A-participated modification of lncRNAs. It is reported that m6A-modified MALAT1 (at A2577) is adequate for the binding of HNRNPC, one of the m6A readers which is essential for pre-mRNA processing [41]. Similarly, m6A methylation (at A2515) increases the accessibility of MALAT1 for RNA-binding protein (RBP) through exposing its purine-rich sequences. Then HNRNPC, which governs gene expression and alternative splicing, binds to MALAT1 using its low-complexity region [42]. In addition, the putative m6A writer METTL16 can interact with the U6 snRNA, pre-mRNAs and lncRNAs, such as MALAT1 [31]. To be specific, the 3’ triple helix domain of MALAT1 is the binding site of METTL16 [127]. Jin et al. demonstrate that METTL3-guided m6A modulation contributes to the elevated expression of MALAT1 with the support of YTHDF3 in non-small cell lung cancer (NSCLC) [128]. Then MALAT1 sponges miR-1914-3p to increase YAP activity and strengthen the metastatic potential of NSCLC.

XIST is another well-characterized mammalian lncRNA. It is the master regulator of X-chromosome inactivation (XCI), a dosage compensation process to balance X-linked gene expression via the suppression of transcription [129]. Moindrot et al. employ a pooled shRNA screen to reveal that WTAP is one of key factors for XIST-mediated silencing, which co-localizes with XIST RNA in nuclear perichromatin spaces [130]. Moreover, a following study demonstrates that XIST is heavily m6A methylated, and highlights the role of m6A modification in XIST-dependent transcriptional silencing [28]. WTAP and METTL3 can be recruited by RBM15/15B to achieve the m6A modification on XIST. Then m6A-marked XIST is recognized by the reader YTHDC1, which promotes XIST-mediated gene inhibition [28]. In addition, SPEN is a vital orchestrator of XCI by binding to XIST. The SPOC domain of SPEN is clarified to be involved in the recruitment of m6A machinery to XIST [131]. Nevertheless, Nesterova et al. have conducted the systematic allelic analysis of XIST-mediated suppression in two interspecific mice models, and put forward the viewpoint that RBM15-centered m6A complex may provide minor contribution to this type of gene silencing [132]. The possible causes for different consequences might rely on the redundancy of m6A modification and the various approaches to assay transcriptional inhibition. Although whether m6A can indeed control XIST-guided silencing is controversial, METTL14/YTHDF2 axis is feasible for regulating the stability of XIST [133]. Therefore, the sophisticated m6A-XIST interaction deserves further explorations.

Actually, there are many other m6A-bearing lncRNAs which have been reported in multiple tumors with the major mechanisms of RNA stability regulation. The lncRNA FAM225A is overexpressed in nasopharyngeal carcinoma, and m6A modification is identified on FAM225A enhancing its RNA stability [134]. In HCC, METTL3-mediated modulation contributes to the stabilization of LINC00958 which intensifies the HCC lipogenesis [135]. Similarly, LNCAROD is up-regulated by METTL3/METTL14 in head and neck squamous cell carcinoma (HNSCC) and impels its tumorigenicity through preventing YBX1 from degradation [136]. VIRMA induces aggressive phenotype of prostate cancer through sustaining m6A levels and abundance of the oncogenic lncRNAs CCAT1/2 [137]. DANC, initially recognized as an anti-differentiation lncRNA, is strengthened by IGF2BP2 based on an m6A-modified site, and boosts stemness like properties of pancreatic cancer [52]. ALKBH5-guided m6A demethylation enhances the expression of PVT1 with the assistance of YTHDF2 in osteosarcoma [138]. In epithelial ovarian cancer, METTL3 increases the level of RHPN1-AS1 [139]. Besides, there are several studies about m6A-related lncRNAs in CRC. RP11 promotes the dissemination of CRC cells by regulating the epithelial mesenchymal transition (EMT). Specifically, the expression of RP11 is collaboratively regulated by METTL3 and ALKBH5. Elevated RP11 recruits the hnRNPA2B1 which recognizes and stabilizes the mRNAs of Siah1 and Fbxo45, thereby preventing the Siah1 and Fbxo45-dependent proteasomal degradation of Zeb1 [140]. Moreover, a study demonstrates a regulatory loop between lncRNA and m6A. LncRNA GAS5 combines with the WW domain of YAP and promotes YAP degradation via modulating its nucleo-cytoplasmic translocation. During CRC tumorigenesis, the m6A reader YTHDF3 interacts with m6A-modified GAS5 and promotes its decay, thus inhibiting the degradation of YAP. Accumulating YAP further activates the transcription of YTHDF3. This is a complicated but intriguing negative feedback loop between m6A and lncRNA [141].

Furthermore, other regulatory layers contain the m6A-mediated translation and the RBP-binding of lncRNA. LINC00278 is an m6A-methylated transcript regulated by METTL3/METTL14/WTAP and
ALKBH5. Studies have revealed that LINC00278 encodes a tumor-suppressing micropeptide called YY1BM, which suppresses the combination of YY1 and androgen receptor, rendering ESCC cells more sensitive to nutrient deprivation. Mechanistically, m^6^A modification promotes the translation of YY1BM via a YTHDF1-dependent manner [65]. *pncRNA-D* is an irradiation-triggered lncRNA which interacts with RBP TLS/FUS. The interaction of *pncRNA-D* with TLS is associated with CCND1 inhibition. METTL3 is responsible for the half-time of m^6^A-methylated *pncRNA-D*. YTHDC1 competitively inhibits the binding of *pncRNA-D* to TLS, thereby alleviating TLS-mediated suppression of CCND1. The decrease of m^6^A modification leads to a G0/G1 arrest in the cell cycle relying on CCND1 [142].

In addition to tumorigenesis, m^6^A-lncRNA interaction is involved in other cellular procedures as well. Yang et al. find that linc1281 is indispensable for appropriate mouse ESC differentiation. The METTL3-dependent m^6^A mark in the last exon of linc1281 is responsible for not only its functional roles, but also the interactions with pluripotency-related miRNAs [143]. For immune homeostasis regulation, m^6^A-modified Inc-Dpf3 controls the migration of dendritic cell (DC). It is well-accepted that although rapid DC migration is vital for initiation of immune defense, timely cessation of its trafficking is also indispensable for the avoidance of excessive inflammation. In the early stage, CCR7-mediated DC migration accelerates in response to CCL19/CCL21. However, during the late stage, CCR7 stimulation triggers the expression of Inc-Dpf3 by removing its m^6^A methylation and protecting it from YTHDF2-mediated degradation. Then Inc-Dpf3 binds to HIF-1α to suppress the HIF1α-dependent glycolysis and the migratory capacity of DC [144].

**IncRNA-m^6^A**

Apart from the m^6^A-lncRNA interaction, IncRNA is able to impact the m^6^A methylation as well. In CRC, LINRIS maintains the stability of the m^6^A reader IGF2BP2 through blocking its ubiquitination/autophagy-lysosome pathway, which facilitates MYC-mediated glycolysis [145]. Moreover, the antisense lncRNA may reinforce the interaction of parent transcripts (mature or nascent) with m^6^A enzymes to control gene expression. For example, the up-regulation of ARHGAP5 is associated with chemoresistance in gastric cancer. In the nucleus, ARHGAP5-AS1 enhances the transcription of ARHGAP5 by binding to its promoter. Furthermore, ARHGAP5-AS1 can recruit METTL3 in the nucleus to induce the elevated m^6^A modification on ARHGAP5 mRNA, eventually facilitating the stability of ARHGAP5 [146]. Similarly, GAS5-AS1 enhances the stability of GAS5 by interacting with ALKBH5 which eliminates m^6^A modification in cervical cancer [147]. In addition, FOXM1-AS increases the binding of ALKBH5 to FOXM1 pre-mRNA in glioblastoma. ALKBH5-triggered demethylation impels the effects of RNA-binding protein HuR, contributing to the elevated level of FOXM1 [148]. GATA3-AS promotes the interaction of KIAA1429 with GATA3 pre-mRNA in HCC [149]. Recently, a study by Zhu et al. reveals another interesting regulatory mode. LncRNA LINC00266-1 can encode a small peptide which tightly interacts with IGF2BP1. The binding of peptide strengthens the recognition of IGF2BP1 on m^6^A-modified RNAs like c-Myc, further enhancing the stability of targets which are closely associated with CRC tumorigenesis [150].

**m^6^A-circRNA**

CircRNA is a species of covalently closed and evolutionally conservative circular transcript, mainly deriving from back-splicing of exons [151]. The structure of circRNA is quite stable. It is broadly expressed in various kinds of specimens via a cell or tissue-specific manner. CircRNA is extensively involved in biological processes, such as developmental modulation, pathogenesis of heart diseases, chemoresistance and tumorigenesis [152]. It primarily functions as the sponge of miRNAs (ceRNA), as well as participates in the interaction with protein, transcription, splicing regulation, and even the non-canonical translation [153].

The information of m^6^A-modified circRNAs is finite but attractive. Zhou et al. have established a genome-wide map of m^6^A-circRNAs in hESCs and Hela cells, and revealed the cell-type-specific patterns of m^6^A modification on circRNAs [153]. There are several features about m^6^A-circRNAs. For example, circRNAs containing long single exons instead of multi-exons are more likely to be modified by m^6^A. m^6^A-circRNAs are commonly generated from those exons without m^6^A peaks in mRNAs. Like miRNAs, circRNAs are methylated by METTL3 and recognized by YTHDF1/YTHDF2 [154]. Park et al. prove that both linear and circular m^6^A-marked RNAs can be edited by the YTHDF2-HRSP12-RNase P/MPR axis [155]. CircNSUN2 is an m^6^A-methylated circRNA which promotes the liver metastasis of CRC patients. The m^6^A motif “GAACU” on circNSUN2 is recognized by YTHDC1, which enhances circNSUN2 export from nucleus to cytoplasm (Figure 3E) [156].

It is inspiring to observe that circRNAs possess widespread m^6^A modification, which is adequate to drive protein synthesis with even a single m^6^A site. This cap-independent translation requires the
assistance of eIF4G2 and YTHDF3 [157, 158]. As expected, the translation can be abolished by FTO, while enhanced by METTL3 or METTL14 [157]. Besides, circE7 is identified as an m^6A-marked, cytoplasmatic and polysomes-associated circRNA. E7 oncoprotein is produced from the translation of circE7 human papillomavirus, while the mutation of possible m^6A motifs strongly suppresses E7 protein expression [159]. Timoteo et al. reveal that METTL3 regulates the m^6A levels while YTHDC1 impacts the back-splicing of circRNAs. The cooperation of METTL3 and YTHDC1 regulates the biogenesis of various circRNAs including circ-ZNF609 which is translatable. Moreover, YTHDF3 and eIF4G2 recognize circ-ZNF609 to regulate its translation (Figure 3F) [158]. Tang et al. identify that approximately half of spermiogenesis-related circRNAs are created via the back-splicing at m^6A-enriched sites in linear mRNAs where start and stop codons are usually located. The outcome is that these circRNAs embrace m^6A-associated open reading frames (ORFs) in their junctions, which reveals the novel role of m^6A in coding-circRNAs biogenesis [160]. These results enrich the m^6A-based non-canonical functions of circRNAs.

In addition, m^6A-circRNAs are also involved in the immunoregulation and environmental stress response (Figure 3G). Foreign circRNAs, instead of self-counterparts, are efficient to trigger T cell activation and antitumor immunity in vivo. The m^6A methylation patterns of exogenous and endogenous circRNAs are quite distinct. Mechanistically, unmodified foreign circRNAs heavily stimulate MAVS polymerization and interferon production after the RIG-I recognition. Nevertheless, m^6A modification impairs activation of immune genes induced by endogenous circRNAs to prevent aberrant responses, which means that m^6A can be the identity for self circRNAs. YTHDF2 is required for the suppression of circRNA-mediated innate immune signaling [161]. Intriguingly, a transcriptome-wide profiling of m^6A-circRNAs is revealed based on the hypoxia mediated pulmonary hypertension (HPH) model. The m^6A abundance of circRNAs is diminished but its expression is increased in hypoxia. m^6A-circRNAs are predominantly derived from encoding transcripts spliced single exons. Furthermore, the network of circRNA/miRNA/mRNA is also regulated by m^6A in HPH. CircXpo6 and circTmtc3 are both m^6A-modified and then down-regulated in HPH [162].

circRNA-m^6A

However, studies about the functions of circRNAs on m^6A modifications are rare. Recently, a study has revealed the role of circRNA-modulated m^6A machinery in major depressive disorder (MDD) [163]. CircSTAG1 is down-regulated in MDD animal models or patients with MDD. CircSTAG1 has the capacity to capture ALKBH5 to reduce its translocation into the nucleus. Then m^6A modification is enhanced, which results in an increased degradation of fatty acid amide hydrolase (FAAH) mRNA and a subsequent decrease in depressive-like behaviors, as well as astrocyte loss. In short, circSTAG1 ameliorates MDD through inhibiting the translocation of ALKBH5 and then augmenting m^6A levels of FAAH mRNA. Further researches should be conducted to elucidate the complex interactions between circRNA and m^6A.

The potential clinical values of m^6A-centered epigenetic modifications

Nowadays, it is generally believed that epigenetic regulations exert a crucial role in the pathogenesis of various diseases. Therefore, exploring the possible pharmaceutical agents targeting epigenetic modifications seems to be a promising therapeutic strategy. For example, it is reported that DNA methyltransferase inhibitor (DNMTi), 5-Aza-2'-deoxycytidine, is able to enhance immunotherapy in esophageal carcinoma by promoting the expression of MAGE-A11 [164]. Moreover, histone deacetylase inhibitor (HDACi) MPT0B291 is capable of suppressing glioma growth partially via facilitating the acetylation of p53 [165]. Interestingly, the synergistic effects on treatment by combining multiple types of epigenetic inhibitors are widely reported [166-168].

In addition, inhibitors based on m^6A-related enzymes have been actively investigated. However, current studies mostly focus on FTO, instead of methyltransferases or m^6A-binding proteins. As a highly selective inhibitor of FTO, meclofenamic acid 2 (MA2) can dramatically suppress the growth and self-renewal of GSC [169, 170]. Chen et al. reveal that R-2HG can inhibit FTO and lead to the decreased stability of MYC and CEBPA, thereby impairing the proliferation of leukemia cells [171]. There are other small molecule drugs targeting FTO that exerted substantial inhibitory effects in tumors, such as FTO-04 [172] and FB23-2 [173]. Moreover, FTO inhibitors participate in the immunotherapy as well. In melanoma, FTO repression promotes tumor growth and increases the response of cancer to anti-PD-1 blockade [174]. Analogously, the freshly recognized inhibitor of ALKBH5, ALK-04, is capable of reinforcing the efficacy of anti-PD-1 therapy [175]. Furthermore, two series of adenine derivatives is identified as the selective inhibitors of METTL3, in
spite of their elusive roles in clinical applications [176].

Notably, the intricate crosstalk between m6A and other epigenetic modifiers is tightly involved in tumor progression as mentioned above. Therefore, abolishing these interplay in human cancers may be the meaningful therapeutic perspective. For example, in gastric cancer, p300-guided H3K27ac modification can trigger the transcription of METTL3, eventually facilitating the malignancy of tumor [73]. Perhaps, combination of HDACi and METTL3 inhibitors may become the feasible approach to interrupt the progression of gastric cancer. In addition, METTL3 mediates the m6A level of MALAT1 to increase its progression of gastric cancer. Furthermore, METTL3 not only controls the level of other RNA modifications such as m5C and A-to-I editing, but also collaborates with them to govern multiple physiological processes. These shed light on the reciprocal associations of m6A and other RNA modifications and pave the way to further comprehend other types of RNA modifications. There is also a close relationship between m6A modification and ncRNAs, including miRNAs, IncRNAs and circRNAs. In most cancers, m6A machinery plays a promoting or suppressive role through altering the expression of targeted ncRNAs. In turn, ncRNAs regulate the stability and expression of m6A-associated enzymes. It breaks the stereotype of ncRNAs and opens up a new paradigm for exploring the potential roles of ncRNAs. Nevertheless, the crosstalk between m6A methylation and circRNAs has not been clearly elucidated, particularly the function of circRNAs on m6A regulation.

Conclusion

m6A RNA methylation, which is a new trajectory of epigenetic modification, has increasingly attracted the attention of researchers over the last few years. Studies have revealed that m6A plays a crucial role in RNA metabolism, such as degradation, alternative splicing, and translation. In addition, the interactions of m6A and targeted RNAs exert great influence on various biological processes, particularly in tumorigenesis. Meanwhile, accumulating evidence has deciphered the interplay between m6A and other epigenetic modulators (DNA methylation, chromatin remodeling, histone modification, RNA modification and ncRNAs), further unveiling the mysteries of epigenetic reprogramming.

Briefly, m6A and DNA methylation may exhibit a cooperative relationship, which relies on the interaction between m6A demethylase and DNA demethylase. In chromatin remodeling, m6A writers or readers are able to regulate the expression of chromatin-related RNAs, thus accommodating the chromatin state. However, there is still a dearth of information regarding the two crosstalk. For example, whether the regulatory loop between m6A and DNA methylation is available deserves further explorations. Notably, the complicated links between m6A and histone modification gradually emerge. m6A methylation modulates the status of histone methylation or acetylation, while histone modification also intends to affect the expression of m6A-related genes. The co-transcriptional regulation expounds the accurate deposition of m6A and histone modification, which determines the precise control of bioprocesses. Furthermore, m6A not only controls the level of other RNA modifications such as m5C and A-to-I editing, but also collaborates with them to govern multiple physiological processes. These shed light on the reciprocal associations of m6A and other RNA modifications and pave the way to further comprehend other types of RNA modifications. There is also a close relationship between m6A modification and ncRNAs, including miRNAs, IncRNAs and circRNAs. In most cancers, m6A machinery plays a promoting or suppressive role through altering the expression of targeted ncRNAs. In turn, ncRNAs regulate the stability and expression of m6A-associated enzymes. It breaks the stereotype of ncRNAs and opens up a new paradigm for exploring the potential roles of ncRNAs. Nevertheless, the crosstalk between m6A methylation and circRNAs has not been clearly elucidated, particularly the function of circRNAs on m6A regulation.

Generally, interactions between m6A modification and other epigenetic members actively participate in the progression of tumors. These crosstalk can not only serve as the essential biomarkers for cancers, but also provide insightful mechanisms to develop the promising therapeutic strategies. Admittedly, these findings are only the tip of the iceberg. In the future, firstly, abundant efforts are still required to uncover more underlying roles of the interplay among these epigenetic modifiers and reach the deeper understanding of epigenetics in cancers. Secondly, it is imperative to explore potential remedies targeting at these interactions to reverse the erroneous epigenetic remodeling and reshape the balance. To be specific, perhaps the combination of m6A enzymes inhibitors and other modifiers inhibitors (DNMTi, HDACi, etc.) deserve validations in multiple tumors. It may be more attracting to directly target at the crosstalk instead of the modification itself. Moreover, it is noteworthy that the associations between FTO and other modifications are poorly investigated. FTO is the most unambiguous drug target with several selective inhibitors. Clarifying the mystery of crosstalk between FTO and other epigenetic members might guide to improve treatment efficiency of cancers.
Abbreviations
ncRNA: non-coding RNA; miRNA: microRNA; lncRNA: long non-coding RNA; circRNA: circular RNA; m6A: N6-methyladenosine; m5C: 5-methyl-cytosine; A-to-I: adenosine into inosine; m6Am: N6'-O-dimethyladenosine; METTL3: methyltransferase-like 3; METTL14: methyltransferase-like 14; WTP: Wilms tumor 1-associated protein; VIRMA: vir-like m6A methyltransferase associated; CBLL1: Cbl proto-oncogene like 1; RBM15: RNA-binding motif protein 15; ZC3H13: zinc finger CCHC domain-containing protein 13; FTO: fat mass and obesity-associated; ALKBH5: alkB homolog 5; YTH: YT521-B domain protein 2.

Competing Interests
The authors have declared that no competing interest exists.

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