RNA m^6^A Modification in Cancers: Molecular Mechanisms and Potential Clinical Applications

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GRAPHICAL ABSTRACT

PUBLIC SUMMARY

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- The dysregulation of m^6^A may lead to tumorigenesis and progression.
- m^6^A regulators may function as potential clinical therapeutic targets for cancers.
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N^6-Methylenadenosine (m^6A) RNA modification brings a new dawn for RNA modification researches in recent years. This posttranscriptional RNA modification is dynamic and reversible, and is regulated by methylases (“writers”), demethylases (“erasers”), and proteins that preferentially recognize m^6A modifications (“readers”). The change of RNA m^6A modification regulates RNA metabolism in eucaryon, including translation, splicing, exporting, decay, and processing. Thereby the dysregulation of m^6A may lead to tumorigenesis and progression. Given the tumorigenic role of abnormal m^6A expression, m^6A regulators may function as potential clinical therapeutic targets for cancers. In this review, we emphasize the underlying mechanisms of m^6A modifications in tumorigenesis and further introduce the potential m^6A regulators-associated therapeutic targets for tumor therapy.

KEYWORDS: N6-methylenadenosine; cancer; RNA methylation; therapy

From the 1950s, an increasing accumulated number of chemically modified nucleosides in RNA have been identified, which change the RNA structures, leading to different biological functions.1,2 Many RNA modifications have been identified in eukaryotic transcripts (Figure 1). N^6-Methylenadenosine (m^6A) RNA modification defines as a methylation of adenosine at the N^6 position, brings a new dawn for RNA modification research since its first discovery in 1974.3 m^6A has been identified as the most abundant mRNA modification, widely distributing in the majority of eukaryotic species including mammals,3–5 plants,6 insects,7 yeast,8 and certain viruses.9,10 The identification and characterization of “writer,” “eraser,” and “reader” proteins, and development of high-throughput sequencing provide new insight into RNA modification biology, especially m^6A RNA modification.12–14

m^6A was identified in about one-third of the mRNA in mammals while an average number of 3 to 5 m^6A modifications were found in each mRNA. Of note, a lot of m^6A sites are evolutionally conserved between humans and mice. The deposition of m^6A modification in the transcriptome is not random.15 A characteristic DRACH sequence (D = G, A, or U, R = G or A, H = A, C, or U) often enriched in the 3′ untranslated region (3′ UTR) and the coding sequence (CDS) when m^6A modification occurs.12,13 Besides, it has clearly known that m^6A modifications exist on almost all types of coding and non-coding RNAs (ncRNAs) and dynamically regulate their relevant molecular processes, physiological and pathological functions.

In this review, we emphasize the underlying mechanisms of m^6A modifications in tumorigenesis and further introduce the potential m^6A regulator-associated therapeutic targets for tumor therapy.

Dynamic Regulation of m^6A

The RNA m^6A modifications are dynamically and reversibly regulated by two important catalytic proteins, methyltransferases and demethylases, which are also recognized as “writers” and “erasers,” respectively. In addition, a set of binding proteins (“readers”) function as decoding the m^6A modifications and recruiting downstream functional complexes (Figure 2).

m^6A Writer Proteins

The RNA m^6A modification writer proteins are a kind of methyltransferase, consist of methyltransferase-like 3 (METTL3), methyltransferase-like 5 (METTL5), methyltransferase-like 16 (METTL16), zinc-finger CCHC-type containing 4 (ZCCHC4), and additional partner proteins such as methyltransferase-like 14 (METTL14), Wilms tumor 1-associating protein (WTAP), Vir like methyltransferase associated (VIRMA), zinc-finger CCHC-type containing 13 (ZC3H13), and RNA-binding motif 15/15B (RBM15/15B).16–21 METTL3 was found acting as the key methyltransferase for m^6A methylation in 1997 and abnormal expression of METTL3 often affects the total level of m^6A methylation.22–24 Meanwhile, METTL14 functions as a synergistic partner for METTL3, which has structural support for METTL3 when they combine into a core methyltransferase complex, and therefore facilitates RNA binding.24,25 The main function of WTAP is binding to METTL3/METTL14 complex and is necessary for the recruitment of optimal substrate and the localization of METTL3/METTL14 complex.26,27 RBM15/15B has been confirmed, helping the combination process between METTL3 and WTAP by specific binding to U-rich regions.27 HAKAI, also known as Cbl Proto-Oncogene Like 1 (CBL1), assists controlling nuclear m^6A methylation. The function of ZC3H13 is similar to CBL1, which helps nuclear localization.27 VIRMA is very important for m^6A modification, especially locating at the 3′-UTR and around stop codon sequences.19

Of all the m^6A methyltransferases, METTL3, METTL16, and ZCCHC4 could function independent of other methyltransferase proteins. As for METTL5, it has been identified as a kind of independent m^6A methyltransferase, catalyzing m^6A on some certain structured RNAs, including 18S rRNA, 28S rRNA, and other small ncRNAs.
The Innovation

At the same time. Unlike the numerous types of m6A writer proteins, only a limited number of m6A demethylase proteins have been identified. A recent study showed that NADP directly binds FTO, independently increases FTO activity, promoting the demethylation of RNA m6A modifications and adipogenesis. The discovery of FTO proves the process of m6A methylation is reversed and controlled under physiological and pathological status.

Another eraser protein is ALKBH5, which has functional similarity with FTO in m6A demethylation. ALKBH5 is widely expressed in various tissues, especially in the testes. The differential expression of FTO and ALKBH5 among different tissues reveals that the two proteins each play their roles in different biological pathways. Specifically, m6A is the only known substrate of ALKBH5 to date. Even more encouraging is the crystal structures of ALKBH5 have been analyzed, providing new insights into the underlying mechanisms for the procedures of m6A recognition and demethylation. The above findings greatly accelerate the development of targeted drugs for m6A demethylation inhibitors.

m6A Reader Proteins

The m6A-mediated posttranscriptional gene regulation has been further understood by identification and characterization of m6A readers. The m6A reader proteins control the destinies of the modified RNAs. Therefore regulation of the proteins may cause misconception of the binding modified RNAs and following RNA metabolic disturbance. The m6A reader proteins consist of the YTH domain family proteins (YTHDF1-3), YTH domain containing proteins (YTHDC1-2), insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs), and heterogeneous nuclear ribonucleoproteins (HNRNPs, including hnRNPA2B1, hnRNPC, and HNRNPG).

The CCR4-NOT deadenylase complex mediates deadenylation of m6A modified RNAs. Cytoplasmic YTHDF2, interacting with the SH domain of the CNOT1 subunit, recruits the CCR4-NOT complex and subsequently destabilizes m6A modified RNAs, leading to their deadenylation and decay. On the contrary, the other two YTH domain family proteins, YTHDF1 and YTHDF3, are reported to facilitate translation by recruiting translation initiation factors. In addition, YTHDF3 accelerates mRNA translation in conjunction with YTHDF1 and promotes the deadenylation and decay of m6A modified RNAs collaboratively with YTHDF2.

**m6A Eraser Proteins**

The m6A eraser proteins, acting as demethylase, remove m6A modifications by raising ferrous iron as co-factor and α-ketoglutarate as co-substrate at the same time. Unlike the numerous types of m6A writer proteins, only two m6A demethylases, including fat mass and obesity-associated (FTO) protein and AlkB homolog 5 (ALKBH5) protein, have been identified so far. In addition, m6A eraser proteins often work in the nucleus where the process of demethylation occurs.

FTO, the first recognized m6A eraser protein, belongs to AlkB family, which can mediate m6A modification by demethylating only internal m6A but also N6, 2'-O-dimethyladenosine (5' cap m6Am) mRNA. Besides, FTO is nucleus localized to a large extent and regulates metabolism, and of course reversible m6A modification plays an important role in these processes. A recent study showed that NADP directly binds FTO, independently increases FTO activity, promoting the demethylation of RNA m6A modifications and adipogenesis. The discovery of FTO proves the process of m6A methylation is reversed and controlled under physiological and pathological status.

Another eraser protein is ALKBH5, which has functional similarity with FTO in m6A demethylation. ALKBH5 is widely expressed in various tissues, especially in the testes. The differential expression of FTO and ALKBH5 among different tissues reveals that the two proteins each play their roles in different biological pathways. Specifically, m6A is the only known substrate of ALKBH5 to date. Even more encouraging is the crystal structures of ALKBH5 have been analyzed, providing new insights into the underlying mechanisms for the procedures of m6A recognition and demethylation. The above findings greatly accelerate the development of targeted drugs for m6A demethylation inhibitors.
In the cell nucleus, YTHDC1 regulates mRNA splicing through recruiting and combining a certain splicing factor serine/arginine-rich splicing factor 3 (SRF3).50 Besides, YTHDC1 also helps mRNA exportation from nucleus to cytoplasm.51 Recently, YTHDC1 has been found to accelerate the decay of a subset of m6A modifications on chromosome-associated regulatory RNAs (carRNAs), especially the long interspersed element-1 (LINE1) elements, via the nuclear exosome targeting complex-mediated nuclear degradation.52 YTHDC2 enhances the translation efficacy of target RNAs while decreasing their abundance in the cytoplasm.53

Currently, IGF2BPs are demonstrated to maintain the stable structures of target mRNA by m6A-dependent approaches under both normal and stressed circumstances.54 HNRNPA2B1 recognizes the m6A signals of primary microRNA and interplays with DiGeorge syndrome critical region gene 8 (DGCR8), while selective recognition of m6A-dependent splicing in mRNA secondary structures was proven as the function of HNRNPC.55–59

m6A in Cancer

Previous studies have suggested the effects of m6A modification and its capacity to modulate and coordinate gene expression. The level of m6A may profoundly affect the characteristics of cancer. It is suggested that m6A may play an important role in carcinogenesis or inhibition in malignant tumor effect. Some proteins need to be modified by m6A to participate in the mechanism of carcinogenesis, but it is still not clear whether they take effect in the modification. The main causes of tumorigenesis in m6A-dependent manner (Figure 3) and the functions of the main m6A proteins in most of the tumor types (Figure 4) are shown.

Acute Myeloid Leukemia. Acute myeloid leukemia (AML) has obvious genetic variation due to uncontrolled proliferation and cell differentiation defects of myeloid leukocytes. So far, the treatment for AML is still unsatisfactory. Previous studies have demonstrated that METTL3 and METTL14 promoted the translation of MYC, MYB, BCL2, SP1, and PTEN, increasing the level of phosphorylated AKT.60,61 It has been found that FTO played an important role in the proliferation of AML cells.62–66 FTO can enhance leukemia oncogene-mediated cell transformation and leukemia, inhibit all trans retinoic acid–mediated differentiation of AML cells, and regulate the mRNA synthesis of target genes (such as ASB2 and RARA) by down-regulating the level of m6A.66 Su et al.55 found that R-2HG inhibited the proliferation of leukemia cells and resulted in cell-cycle arrest by inhibiting FTO activity, increasing m6A modification, reducing the stability of MYC/CEBPA transcription. Many studies have confirmed that YTHDF2 can promote tumor progression. Paris et al.67 suggested that YTHDF2 was highly expressed in AML and played a key role in the initiation and proliferation of AML. They found that targeting YTHDF2 could prolong the half-life of the m6A modified transcripts, thus selectively destroying the initiation and proliferation of AML without affecting normal hematopoiesis. Besides, WTAP is upregulated in AML and the high expression of WTAP predicts poor outcomes in patients with AML.68,69

Glioblastoma. Glioblastoma (GBM) is the deadliest primary brain tumor.70 Research on the role of METTL3 in GBM has produced conflicting conclusions. The different phenotype associated with METTL3 can be illustrated by the different dependence and genetic heterogeneity of m6A modified RNA in different types of GBM cells. Cui et al.71 demonstrated that METTL3 and METTL14 inhibit the growth and tumorigenesis of glioblastoma stem-like cells (GSCs) by down-regulation of ADAM19/EPHA3/KLF4 pathway. ALKBH5 was also highly expressed in GSCs.72,73 Silencing ALKBH5 could inhibit the proliferation of GSCs. ALKBH5 can induce demethylation of

![Image](https://example.com/image.png)

**Figure 2. Mechanism of RNA m6A Modifications** The m6A modification is catalyzed by the "writer" proteins including METTL3, METTL14, WTAP, METTL5, METTL16, ZCCHC4, VIRMA, RBM15/15B, HAKAI, and ZC3H13. The m6A methylation is removed by "eraser" proteins FTO or ALKBH5. "Reader" proteins recognize m6A modifications and determine targeted RNA destiny.
FOXM, a transcription factor, and stimulate cell proliferation, resulting in increased FOXM1 expression. Inhibiting the expression of ALKBH5 provides a new direction for the treatment of glioma. Visvanathan et al. found that METTL3 was highly expressed in malignant GBM. METTL3 promoted tumor growth by targeting the 3’ UTR of Sox2 mRNA. Silencing METTL3 can inhibit tumor growth and enhance tumor radiosensitivity, which can be used as a potential molecular target for GBM therapy. Similar to AML, the high expression of WTAP also predicts poor prognosis in patients with GBM.

Lung Cancer. Lung cancer is the leading cause of cancer-related mortality worldwide. METTL3 is the oncogene of lung cancer through different mechanisms. Lin et al. found that METTL3 can enhance RNA translation without the aid of methyltransferase and reader protein activity. METTL3 increases RNA translation by directly recruiting translation initiation factors. METTL3 increases the growth, survival and invasion of lung adenocarcinoma cells by increasing EGFR and TAZ. Choe et al. demonstrated that METTL3 could enhance translation, transform oncogenes, and form dense polyribosomes by interacting with EIF3H in primary lung cancer, which can be applied as a potential therapeutic target. METTL3 can also promote tumor progression by regulating some microRNAs (miRNAs). Du et al. found that mir-33a can inhibit the proliferation and invasion of non-small cell lung cancer (NSCLC) by targeting METTL3 mRNA. Wei et al. revealed that mir-600 can inhibit the migration and proliferation of lung cancer cells by down-regulating the expression of METTL3. Li et al. found that FTO promotes the proliferation of NSCLC by increasing the expression of USP7. Liu et al. found that overexpression of FTO can down-regulate the level of m^6^A in MZF1 mRNA transcripts, increase the stability of mRNA, and promote the expression of MZF1, leading to the proliferation and invasion of lung squamous cell carcinoma cells. In addition, m^6^A demethylase ALKBH5 was indicated to inhibit tumor growth and metastasis in patients with NSCLC by reducing the expression of YTHDF-mediated YAP, whereas some studies suggested ALKBH5 promoted the progression of NSCLC.

Endometrial Cancer. Approximately 70% of patients with endometrial cancer show decreased m^6^A expression level because of either reduced expression of METTL3 or mutation (loss-of-function) in METTL14 and the tumorigenicity is associated with activation of the AKT pathway. Down-regulation of METTL14 can reduce the level of m^6^A of RNA. Recent studies have shown that the decrease of m^6^A level is associated with endometrial cancer caused by METTL14 gene mutation. They found that the deletion of METTL14 increased cancer cell proliferation, clone formation, and metastasis. They observed that the level of m^6^A in tumor tissue was lower than that in adjacent normal tissue. They believe that the METTL14 mutation reduces the level of m^6^A, which plays a key role in the progression of endometrial cancer. Liu et al. also found that the down-regulation of METTL14 could lead to the decrease of the expression of PHLP2, the negative regulator of AKT pathway, and increase the expression of mTORC2, the positive regulator of AKT pathway, which led to the proliferation of endometrial cancer cells. FTO can also participate in the occurrence and development of endometrial cancer through a variety of mechanisms. Zhu et al. have shown that estrogen induces FTO nuclear aggregation through the mammalian target of Rapamycin signaling pathway, thus enhancing the proliferation and activity of endometrial cancer cells and promoting tumor progression. Another study showed that estrogen induces overexpression of FTO gene by activating PI3K/AKT and MAPK signaling pathways, which leads to the proliferation and invasion of endometrial cancer cells.
The role of FTO in cervical cancer tumorigenesis has been uncovered. FTO functions as an oncogenic regulator for cervical cancer in terms of promoting tumor cell proliferation and migration by regulating E2F1 and Myc transcripts. Long ncRNA GAS5-AS1 was found having a lower expression in cervical cancer when compared with that of adjacent normal tissues and played its role on YTHDF2-dependent pathway. Besides, m6A "reader" IGF2BP family proteins were also reported serving as carcinogenic roles in CVC.

Ovarian Cancer. METTL3 promotes the maturation of miR-126-5p and therefore accelerates ovarian cancer (OVC) progression. In addition, another study demonstrated that METTL3 facilitated OVC growth and invasion via activating epithelial to mesenchymal transition. The expression of ALKBH5 was found to be increased in epithelial OVC tissues when compared with the normal ovarian tissues and ALKBH5 was identified as a candidate oncogene in epithelial OVC. The "reader" protein IGF2BP1 enhanced SRC/MAPK-driven invasive growth of OVC cells and the high expression of IGF2BP1 was related to poor prognosis of patients with OVC. Most recently, recruitment of YTHDF1 to m6A-modified TRIM29 was participated in accelerating TRIM29 translation in the OVC cells with cisplatin-resistance, which would be a potential therapeutic target.

Breast Cancer. There is now a compelling body of evidence demonstrating that epigenetic modifications including RNA m6A modification play a vital role in the tumorigenesis and progression of breast cancer. Cai et al. found that METTL3 interacts with hepatitis B x-interacting protein (HBXIP) in breast cancer cells, and HBXIP inhibits the expression of METTL3 by acting on 3'UTR of miRNA let-7g. At the same time, METTL3 promoted the expression of HBXIP through m6A modification. A positive feedback loop was formed between HBXIP/miRNA let-7g/METTL3, which promoted the proliferation of breast cancer cells. METTL14 was promoted by LINC00942, further study showed that METTL14 interacted with DGC8 and positively regulated the expression of breast cancer cells. METTL14 may regulate the expression of miRNA 126 through the modulation of m6A, and then regulate its downstream target to inhibit the metastasis of liver cancer cells in mice. According to these results, they speculated that METTL14 may regulate the expression of miRNA 126 through the modulation of m6A, and then regulate its downstream target to inhibit the metastasis of liver cancer cells in mice. Consequently, they found that HIFs promoted the invasion and metastasis of breast cancer cells by regulating ZNF217 to inhibit methylation and ALKBH5 induced demethylation.

Colorectal Cancer. Epigenetic alterations exist in various aspects of colorectal tumorigenesis. In colorectal cancer, METTL3 acts as a functional oncogene in an m6A-IGF2BP2/3-dependent manner. Oncogene c-Myc can promote the expression of YTHDF1, induce the proliferation and metastasis of cancer cells, and increase their resistance to chemotherapy drugs. Knockdown of c-Myc can inhibit the expression of YTHDF1, inducing the proliferation and metastasis of cancer cells, and increasing their resistance to chemotherapy drugs. YTHDF3 negatively regulated IncRNA GAS5 through GAS5-YAP-YTHDF3 axis both in vivo and in vitro. The expression of YTHDC2 is positively correlated with the stage and metastasis of colon cancer. Knockdown the expression of YTHDC2 can inhibit the metastasis of tumor cells in vivo and in vitro through HIF-1α. Except all the preceding m6A-associated oncogenes, METTL14 is demonstrated as a tumor suppresser, decreasing the proliferation and tumor metastasis of colorectal cancer via different molecular mechanisms.

Hepatocellular Carcinoma. Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver. Chen et al. found that METTL3 can promote the progression of liver cancer cells through YTHDF2-dependent transcriptional regulation of SOCS2 silencing. Further study showed that METTL14 interacted with DGC8 and positively regulated the expression of miRNA 126. Overexpression of METTL14 can inhibit the metastasis of liver cancer cells in mice. According to these results, they speculated that METTL14 may regulate the expression of miRNA 126 through the modification of m6A, and then regulate its downstream target to inhibit the metastasis of HCC. Therefore, METTL14 may be an important adverse prognostic factor for HCC. As for IGF2BP family, IGF2BP1, IGF2BP2, IGF2BP3, and IGF2BP4 were found to be involved in the regulation of liver cancer progression through interacting with HIF-1α.
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and IGFBP3 were all identified as oncogenes to promote the carcinogenesis of HCC. YTHDF2 not only acts as a tumor activating protein, but also acts as a tumor suppressor protein. Some studies have shown that hypoxia can induce the decrease of the expression of YTHDF2 in hepatocellular carcinoma. They also found that overexpression of YTHDF2 inhibited the proliferation of HCC cells and activated MEK and ERK. YTHDF2 can directly act on the 3’UTR m6A modification site of EGFR mRNA, resulting in the degradation of EGFR mRNA. In addition, the phosphorylation of ERK induced by hypoxia was also blocked by YTHDF2, suggesting that hypoxia can down-regulate the phosphorylation of ERK induced by YTHDF2. YTHDF2 inhibits ERK/MAPK signal transduction by reducing the stability of EGFR mRNA in HCC, thus inhibiting the proliferation of hepatoma cells. WTAP was examined to determine whether it was related to clinicopathological factors of patients with HCC, and the results showed that the expression level of WTAP was increased more in HCC than in para-carcinoma tissues and associated with worse prognosis. Besides, VIRMA was also defined as an oncogene in HCC.

Pancreatic Cancer. Pancreatic cancer is recognized as a kind of high-grade malignant neoplasm. He et al. revealed that ALKBH5 may be a potential therapeutic target for pancreatic cancer by down-regulating methylation of lncRNA KCNK15-AS1 in pancreatic cancer cells and inhibiting cell motility. Taketo et al. found that pancreatic cancer cells with low METTL3 expression are more sensitive to chemotherapeutic drugs such as gemcitabine, 5-fluorouracil, and cisplatin and radiotherapy, it provides a potential target for the treatment of pancreatic cancer. Many studies have proved that IFG2BP2 was overexpressed in pancreatic cancer and promoted cancer proliferation. A case-control study demonstrated that variants in the FTO gene was associated with pancreatic cancer risk. YTHDF2 promoted proliferation while inhibiting migration and invasion in pancreatic cancer cells.

Gastric Carcinoma. With improved diagnostic strategy, patients who diagnosed with early-stage gastric carcinoma (GC) is increasing. Previous studies have shown that epigenetics may play an important role in the genesis and growth of GC. Li et al. demonstrated the high expression of FTO and ALKBH1 mRNA indicates poor prognosis of GC through mining TCGA database. METTL3 promotes GC angiogenesis and glycolysis by increasing the stability of HDGF mRNA and activating the AKT signaling pathway. ALKBH5 promotes invasion and metastasis of GC by decreasing methylation of the lncRNA NEAT1. Some studies demonstrated that IFG2BP3 functioned as an oncogene to promote tumor progression in GC. Knockdown of METTL14 (m6A suppression) promotes GC development through activating the Wnt/PI3K-AKT signaling pathway, whereas increasing m6A levels reversed these phenotypical and molecular changes.

Prostate Cancer. Prostate cancer (PRC) is one of the most common malignant neoplasms. studies have shown that down-regulation of YTHDF2 can inhibit the proliferation and invasion of PRC cells. There was a negative correlation between YTHDF2 and miR-493-3p. Knockout of YTHDF2 could increase the level of miRNA and inhibit the proliferation and invasion of GC cell lines. Besides, METTL3 and VIRMA were also reported promoting the development and progression of PRC in different manners.

Renal Cell Carcinoma. METTL3 and METTL14 can not only promote the proliferation and metastasis of tumor cells, but also inhibit the progress of tumor. Some studies have shown that low expression of METTL3 is associated with larger tumors and higher histological grade in mice. The survival time of renal cell carcinoma patients with METTL3 overexpression was significantly prolonged. WTAP also plays a role in tumor growth by binding with mRNA and enhancing the stability of mRNA. WTAP can combine with cyclin dependent protein kinase (CDK) 2 transcripts, enhancing its stability, delaying cell apoptosis and promoting the proliferation of renal carci-

Potential Applications of Cancer Treatment Based on m6A

Many researchers have demonstrated that m6A has emerged as a widespread regulatory mechanism that controls gene abnormal expression in diverse pathological pathways, leading to tumorigenesis. Therefore, m6A regulators may function as potential clinical therapeutic targets for cancers. Since the first m6A demethylase FTO was identified, FTO has become the most striking target for developing targeted drugs against tumors. Several FTO-targeted inhibitors have already been developed, including MO-I-500, medrofenamin acid (MA), FB23, R-2HG, rhein, and so on. MO-I-500, a selective inhibitor, inhibits the enzyme activity of FTO and was reported to suppress the proliferation of breast cancer cell lines. MO-I-500 also proved to be a selective inhibitor for treating GBM through inhibiting FTO over ALKBH5. Recently, FB23 and FB23-2 were designed as small-molecule FTO inhibitors, which have achieved remarkable inhibitory effect in AML models. As for nonselective inhibitors for FTO, rhein was the first to be uncovered and competitively binds to specific site of FTO. R-2HG, highly expressed by mutant isocitrate dehydrogenase 1/2 (IDH1/2) enzymes, was demonstrated to play important antitumor effect in glioma and leukemia cells.

Multidisciplinary therapy, including neoadjuvant therapy, surgery, adjuvant chemoradiotherapy, targeted therapies, and immunotherapies, has been widely adopted in cancer treatment. However, drug resistance maintains a dominating hindrance to curative treatment, leading to treatment failure and tumor progression. Recently, the dysregulation of m6A regulators has been found related to the advent of treatment resistance. As for immunotherapy, it is an emerging way of dealing with cancer. YTHDF1 was proved to regulate antitumor immunity and had synergetic effect on immunotherapy by improving the therapeutic effect of PD-L1 inhibitor. In addition, Yang et al. found that m6A mRNA demethylation by FTO promoted melanoma growth and suppressed response to anti-PD-1 blockade, which indicated the combination of FTO inhibitors and anti-PD-1 blockade may help to promote sensibilization of immunotherapy in melanoma. Furthermore, the detailed information on drug resistance caused by m6A dysregulation is listed in Table 1. These studies indicated that m6A RNA modification signatures may provide important information for predicting drug resistance and help clinicians to adjust the treatment plan in time.

Conclusions and Future Perspectives

Different from DNA, RNA has much more intricate posttranscriptional processing: RNA splicing, RNA editing, and RNA chemical modifications. RNA chemical modifications, most of which have no influence on nucleoside sequence, are structurally diverse and functionally multiple, indicating their functional importance.

In recent years, epigenetics, especially m6A RNA modification, has been further understood and explored with the rapid advances in detection methods and high-throughput sequencing techniques. It has been widely illustrated that the dysregulation of m6A RNA modification is related to various types of cancers, as well as the drug resistance to anti-tumor therapy. However, as the evidence (m6A plays important role in tumors) began to accumulate, the underlying mechanisms of m6A in cancer still have not yet been fully realized. To be specific, in many kinds of cancers, such as NSCLC, breast cancer, acute myelocytic leukemia, and some gynecological tumors, overexpression of either writer or eraser proteins can play tumorigenesis roles, while controversies of the roles of m6A regulators still exist in other cancer types. Similar to DNA methylation signatures (hmc, 5hmc, and so on), DNA RNA modifications of certain genetic loci could function as biomarkers associated with prognosis, molecular subtyping, and precise diagnosis. Many researchers focus on the identification of m6A-targeted mRNAs in diverse diseases, especially in cancers. Moreover, how m6A RNA modification affects the functions of ncRNAs still remains unclear and ncRNAs have been confirmed having a close link with a wide variety of tumors. carRNAs recently were found to have m6A modifications on them, which were deposited by METTL3, including repeat RNAs, promoter-associated RNAs, and enhancer RNAs. Thus, the direct cross-talk between the m6A carRNA modifications and chromatin state opens a new door on how m6A carRNA modifications regulate transcription.
The Innovation in cancers is an emerging of RNA m6Am exploration and clinical cancer therapies. At present, our understanding of tumorigenesis and cancer progression, but novel strategies for drug treatment resistance and cancer immunity, it is attractive to develop transcriptome editing is also worthy of expectation. Therefore, whether a technology could be developed for epigenetic scissors). Therefore, whether a technology could developed for epitranscriptome editing is also worthy of expectation.

Considering that the dysregulation of m6A regulators is related to treatment resistance and cancer immunity, it is attractive to develop m6A-based targeted drugs for oncotherapy. Besides, m6A-based targeted small-molecule drugs could function as a kind of sensitizer, improving the therapeutic effects of chemotherapy, radiotherapy, and even immunotherapy in the future. In general, RNA m6A modification in cancers is an emerging field of cancer epigenetic research, providing not only new insights into the potential molecular mechanisms of tumorigenesis and cancer progression, but novel strategies for drug exploitation and clinical cancer therapies. At present, our understanding of RNA m6A modifications for cancers is still in its infancy and further studies are desperately required for the rosy scenario.

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| Table 1. m6A Alteration in Drug-Resistant Cancer Cells |
|---|
| **Cancer Type** | **Therapeutic Agents** | **m6A Proteins Involved** | **Change of m6A Proteins** | **Reference** |
| AML | R2HG | FTO | Down-regulate | Su et al. 39 |
| AML | TKI | FTO | Up-regulate | Yan et al. 175 |
| GBM | γ-irradiation | METTL3 | Up-regulate | Visvanathan et al. 174 |
| HCC | Sorafenib | METTL3 | Down-regulate | Lin et al. 176 |
| CRC | Doxorubicin | METTL3 | Up-regulate | Uddin et al. 172 |
| NSCLC | Cisplatin | METTL3 | Up-regulate | Jin et al. 170 |
| NSCLC | Cisplatin | YTHDF1 | Down-regulate | Shi et al. 92 |
| NSCLC | Afatinib | m6A | Up-regulate | Meng et al. 177 |
| NSCLC | Crizotinib | METTL3, WTAP | Up-regulate | Ding et al. 178 |
| PAC | cisplatin, 5-Fu and gemcitabine | METTL3 | | Taketo et al. 136 |
| PRC | Cisplatin | VIRMA | – | Su et al. 179 |
| CSCC | cisplatin, irradiation | FTO | Up-regulate | Zhou et al. 180 |
| OVC | PARP inhibitor | FTO, ALKBH5 | Down-regulate | Fukumoto et al. 181 |
| MLM | anti-PI-3 blockage | FTO, YTHDF2 | Up-regulate | Yang et al. 174 |

AML, acute myeloid leukemia; GBM, glioblastoma; HCC, hepatocellular carcinoma; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PAC, pancreatic cancer; PRC, prostate cancer; CSCC, cervical squamous cell carcinoma; OVC, ovarian cancer; MLM, melanoma.
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