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REVIEW

Advances in the functional roles of N6-methyladenosine modification in cancer progression: mechanisms and clinical implications

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Abstract

N^6-methyladenosine (m^6A), the methylation targeting the N^6 position of adenosine, is the most common internal modification of mRNA in eukaryotes. Considering the roles of m^6A in regulating gene expression, the investigation of m^6A roles in the biological processes including cell renewal, differentiation, apoptosis, and invasion of cancer cells has become a hot research topic. There are three kinds of protein involved in m^6A regulation. The methyltransferases and demethylases cooperatively regulate the m^6A levels, while the m^6A reading proteins recognize the m^6A sites and mediate multiple m^6A-dependent biological functions including mRNA splicing, transfer, translation, and degradation. At present, a large number of studies have found that the changes of m^6A levels in tumor cells play a very important role in the occurrence and development of tumors, as well as metastasis and invasion of tumor cells. This review summarizes the different roles of m^6A modification in the occurrence and development of various cancers, and discusses the possibility of choosing the m^6A related proteins as potential therapeutic targets.

Keywords N^6-methyladenosine · Cancers · Functional roles · Clinical implications

Introduction

The posttranscriptional modifications of mRNA play important roles in regulating a series of physiological processes and disease development, and thus the studies about their function have become the hot topics. Currently, more than 100 RNA modifications have been identified [1]. N^6-methyladenosine (m^6A) is the most common methylation modification in eukaryotic mRNA and long noncoding RNA, and is found in ribosome-related mRNA as well [2]. In addition, m^6A is identified in more than 25% of human mRNAs [3]. As the most common internal modification in mRNA, m^6A modification is generally enriched in 3′-untranslated terminal regions (3′-UTRs) and near stop codons [4]. Zhang et al., developed a new FunDMDeep-m^6A algorithm to detect the dynamic m^6A levels in cells, and confirmed that m^6A modifications could target many important genes involved in biological processes including embryonic development, stem cell differentiation, cell apoptosis, as well as proliferation and metastasis of cancer cells [3].

There are three types of regulatory proteins involved in m^6A occurrence, elimination and function exertion; the methyltransferases (writers) are involved in catalyzing methyl transfer; the demethylase (erasers) can remove m^6A modification; various m^6A reading proteins can recognize and bind to m^6A-modified mRNAs to mediate corresponding functions [5]. It is noted that three kinds of regulatory proteins constitute the molecular basis for m^6A regulation in multiple metabolic processes of RNA.

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The molecular basis for the occurrence, elimination and function of m^{6}A

The occurrence of m^{6}A: m^{6}A writers

The m^{6}A methyltransferase complex is composed of METTL3, METTL14, WTAP, and other auxiliary subunits including VIRMA [6, 7], RBM15 [8], and ZC3H13 [9] (Fig. 1). METTL3 is the catalytic part of the methyltransferase complex, and catalyzes the modification of m^{6}A by cross-linking with *S*-adenosylmethionine [10]. METTL14, one of the most important auxiliary subunits in the methyltransferase complex, combines with METTL3 to form a heterodimer to activate the catalytic function of METTL3. In addition, METTL14 can recognize RNA substrates and then mediate the binding of methyltransferase complex to RNA substrates [6]. WTAP acts as a regulatory subunit to recruit METTL3/14 to the mRNA for subsequent m^{6}A methylation [11]. Previous studies have reported that VIRMA mediates preferential methylation of mRNA near the 3'-UTR and stop codons [7]; RBM15 and RBM15B mediate m^{6}A modification in long non-coding RNA X-inactive specific transcripts (XIST) [8]. Moreover, ZC3H13 has been proved to guide the binding of RNA-binding protein Rbm15 to mammalian WTAP [9]. In addition to the METTL3/14 complex, METTL16 is also one kind of m^{6}A methyltransferases, which mainly functions on a large number of pre-mRNAs and various non-coding RNAs [12].

Elimination of m^{6}A: m^{6}A erasers

m^{6}A modification is actually a dynamically reversible process, as the modification on mRNA can be eliminated via m^{6}A demethylases. There are two known common demethylases of m^{6}A: fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5) (Fig. 1). As a member of the AlkB family, FTO has a highly conserved catalytic domain, which mainly acts on 3′-untranslated region of transcripts to regulate the m^{6}A level. FTO has been found to be of great significance to the m^{6}A modification of whole transcriptome mRNA [13], and closely related to metabolic diseases such as diabetes [14], obesity [15], and ischemic heart failure [16]. ALKBH5, a member of the AlkB family, has been proved to be another one mammalian demethylase [17]. By regulating the m^{6}A levels, ALKBH5 performs biological functions including regulating cell proliferation, migration, invasion, and ossification [18]. Another demethylase ALKBH3, which is relatively less reported, usually preferentially exhibits demethylation activity in ssDNA, and there are also recent studies reporting that it exhibits demethylation activity in tRNA [19].

Recognition of m^{6}A modification: m^{6}A readers

After specifically recognizing the m^{6}A sites of RNA, m^{6}A reading proteins mediate a series of biological functions by modulating splicing, translation, transport, and enhancing or

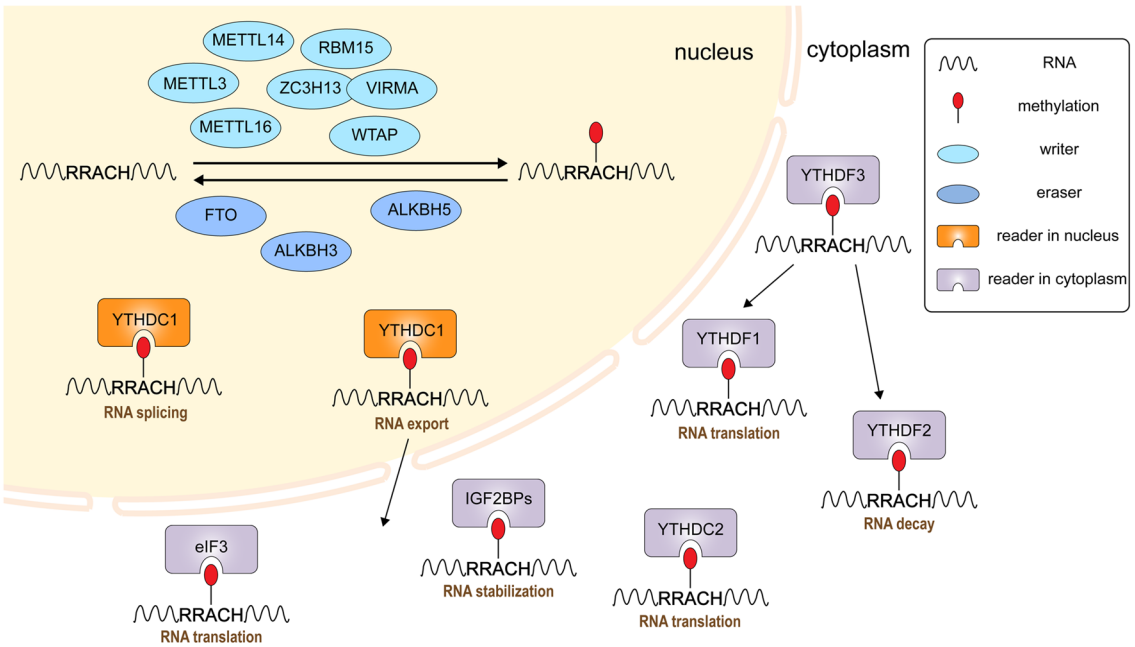

Fig. 1 Functions of m^{6}A effectors. The writers are involved in catalyzing methyl transfer. The erasers remove m^{6}A modification. Reading proteins can recognize and bind to m^{6}A-modified mRNAs to mediate corresponding function

reducing the stability of target mRNAs. The YTH protein family proteins, including YTHDF1, YTHDF2, YTHDF3, YTHDC1 and YTHDC2, have been confirmed as m^6A reading proteins. YTHDF1 promotes translation of target mRNAs, while YTHDF2 reduces the stability of the target transcripts (Fig. 1) [20]. YTHDF3 assists YTHDF1 and YTHDF2 to promote RNA translation and modulate RNA degradation, respectively [21, 22]. YTHDC1, the m^6A reading protein in nucleus, promotes the transport of mRNA from the nucleus to the cytoplasm [23], and also mediates RNA splicing in a concentration-dependent manner [24]. YTHDC2 is also the member of the YTH protein family, which can improve the translation efficiency or reduce the mRNA abundance of target genes [25].

The insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) is a newly discovered m^6A reading proteins. Different from the YTH protein family, IGF2BPs promote expression of target genes by increasing the stability of target mRNAs [26]. Studies have confirmed that eukaryotic initiation factor 3eIF3 can get rid of the assistance of cap complex and independently recruit the 43S ribosomal complex to start translation after binding to the m^6A sites in 5'-UTR of mRNAs, indicating that eIF3 regulates mRNA cap-independent translation after recognizing and binding to m^6A-modified mRNAs [27]. Moreover, METTL3 was also observed to enhance the translation of target mRNAs by activating translation process in human cancer cells [28].

m^6A regulation in the tumors

Acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) is an aggressive and fatal hematological malignancy, characterized by abnormal proliferation of primitive and naive myeloid cells in the bone marrow and the periphery. Epigenetic modifications including DNA methylation and histone modifications play important roles in phenotype maintenance of leukemia cells [29]. METTL3 and METTL14 have been reported to be highly expressed in AML cells relative to hematopoietic progenitor cells, and both exhibit carcinogenic effects [30, 31]. METTL3 induces enhanced expression of SP1 by upregulating the m^6A methylation levels on the oncogenes SP1 and SP2 mRNAs, and SP1 promotes the differentiation of hematopoietic stem cells into AML cells [32]. In addition, METTL3 can promote the expression of c-MYC, BCL-2 and PTEN in AML cells to increase intracellular p-AKT level, thereby promoting proliferation of cancer cells and exerting carcinogenic effects [30]. Weng et al. identified that the SP1-METTL14-MYB/MYC signal axis regulates myeloid differentiation of normal cells and participates in malignant hematopoiesis [31]. In addition, Bansal et al., identified that WTAP plays an important role in the proliferation and differentiation of leukemia cells, and thus WTAP is expected to become a new target for the treatment of AML [33].

Similar to m^6A writers, m^6A erasers also play a role in regulating the occurrence and development of AML, among which FTO and ALKBH5 are abnormally active in various karyotypes of AML [34, 35]. Mechanism studies have found that FTO reduces the m^6A levels of target mRNAs, such as tumor suppressor genes ASB-2 and RARA in the untranslated region, resulting in downregulation of their mRNA stability and thus promoting the AML development [34]. Shen et al. found that ALKBH5, overexpressed in AML, functions as an oncoprotein, and its upregulated expression is associated with poor prognosis of AML [35]. By contrast, Kwok's study indicated that ALKBH5 is reduced in AML cells and suggested that it exhibits a tumor suppressor effect [36]. In another one study, ALKBH5 and YTHDF2 cooperatively regulate the mRNA stability of the receptor tyrosine kinase AXL in a m^6A-dependent manner [37]; AXL overexpression promotes cancer cell proliferation, survival, migration, and invasion by activating PI3K/Akt and MAPK/Erk pathways [38].

Glioblastoma (GBM)

Glioblastoma, originating from poorly differentiated glial cells, is one of the most common malignant tumors in the central nervous system. Cai et al., showed that m^6A methylation modification is involved in the self-renewal of glioblastoma stem cells (GSCs), and pathogenesis and development of tumors. Moreover, Cui et al., further proved that METTL3 and METTL14 can regulate growth of GSCs and GBM progression by down-regulating the expression of oncogenes, such as ADAM19, EPHA3, and KLF4 [39]. However, contradictory results about METTL3 in GBM progression were obtained, which suggested that METTL3 promotes the growth of GSCs by up-regulating SOX2 expression when these cells are exposed to radiation [40]. In addition, METTL3 has also been found to function as a regulator of nonsense-mediated mRNA decay (NMD) to maintain the aggressiveness of tumor [41]. These results suggest that the effects of METTL3 on the pathogenesis and development of GBM are diverse and complex, thus further investigation about METTL3 roles in GBM progression is needed. In glioblastoma, overexpressed ALKBH5 is associated with enhanced ability of tumor stem cells to resist radiation and invasion [42]; mechanistically, ALKBH5 reduces the level of intracellular m^6A methylation and thus promotes the expression of the oncogene FOXM1 to enhance the self-renewal ability and tumorigenicity of GSCs [43]. Moreover, the m^6A reading protein IGF2BP2 is observed to be upregulated in GBM tissues, which promotes the proliferation, migration, invasion and epithelial-mesenchymal transition of GBM

cells by upregulating insulin-like growth factor 2 (IGF2) and then activating PI3K/AKT signaling pathway [44]. As predicted, inhibition of PI3K/AKT pathway can increase the sensitivity of GBM to temozolomide (TMZ) treatment [45]. Collectively, these results suggest that m^{6}A modification mediates the occurrence and migration of GBM, which provides insight into therapeutic strategies by exploiting m^{6}A RNA methylation as targets for treating GBM.

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC), a primary liver cancer with high mortality, is the third most common cause of cancer-related high mortality in the world [46]. Increasing evidences show that HCC is closely related to m^{6}A. The TCGA analyses indicate the overall survival and disease-free survival rate of HCC patients with high METTL3 expression are poor. RNA-Seq assays revealed that METTL3 is significantly upregulated in HBV-related liver cancer tissues relative to corresponding non-tumor (NT) liver tissues. Further studies demonstrated that METTL3 reduces the mRNA stability of the tumor suppressor SOCS2 through the YTHDF2-dependent pathways in HCC, bringing about the pathogenesis and development of HCC [47]. Moreover, Chen et al. determined that Snail, an important transcription factor related to EMT, is a downstream target of METTL3; METTL3 and YTHDF1 jointly promote the transfer of HCC by enhancing translation of Snail protein [48].

METTL14 was examined to be downregulated in HCC [49]. Mechanism studies revealed that METTL14 mediates the recognition and binding of DiGeorge syndrome chromosomal region 8 (DGCR8) to pri-miR-126 through m^{6}A-dependent pathways, resulting in miR-126 maturation [50]. It is noted that miR-126 functions as a tumor suppressor and is downregulated in a variety of tumors [51]. In addition, Li et al. identified that METTL14 might participate in malignant progression of HCC by regulating the m^{6}A modification levels of cysteine sulfinic acid decarboxylase (CSAD), SOCS2, and glutamic-oxaloacetic transaminase 2 (GOT2) [52].

The m^{6}A methyltransferase WTAP, KIAA1429 and the demethylase FTO have also been reported to influence the HCC growth and invasion through different mechanisms [53–56]. FTO has been reported as one tumor-promoting effector or tumor suppressor for the pathogenesis and development of HCC, respectively [55, 56]. Thus, the influences of FTO on the proliferation ability of different HCC cells were controversial, which needs further research and verification. In addition, ALKBH5 was observed to be reduced in HCC. Functional studies further confirmed that ALKBH5 could inhibit the growth and invasion of liver cancer cells in vivo and in vitro. Decreased ALKBH5 increases the m^{6}A modification of LYPD1, which hinders the recognition of m^{6}A-modified LYPD1 by the m^{6}A reading protein IGF2BP1 and thus enhances LYPD1 mRNA stability, resulting in tumor-inducing effect in HCC [57]. The above studies have enriched the understanding of m^{6}A roles in HCC development, and provided different perspectives and insights for the developing effective treatment strategies.

Gastric cancer (GC)

Although the incidence of gastric cancer (GC) has decreased in the past few decades, GC is still the fifth most common malignant tumor in the world [58]. In GC tissues, the expression of METTL3 was significantly increased. Wang et al., found that METTL3 increases the m^{6}A modification levels of *HDGF* mRNA, which are then recognized and bound by IGF2BP3 to upregulate HDGF protein level, promoting tumor angiogenesis and glycolysis and thus accelerating tumor growth [59]. Moreover, a previous study showed that METTL3 downregulation can activate the apoptotic pathway and inactivate the AKT signaling pathway, thereby inhibiting the proliferation and migration of human GC cells [60]. Taken together, it is speculated that METTL3 may be a potential target for the treatment of human GC.

Zhang et al. also confirmed that ALKBH5 can promote the invasion and metastasis of GC by reducing m^{6}A modification levels of the lncRNA NEAT1 [60], suggesting that ALKBH5 and NEAT1 may be potential therapeutic targets for GC.

Compared with the benign gastric disease patients and healthy groups, the m^{6}A levels in the peripheral blood of GC patients were significantly increased with the progress and metastasis of GC; while the m^{6}A levels in the GC patients decreased after surgery. Compared with healthy groups, the expression of ALKBH5 and FTO in the GC patients was significantly down-regulated. These results suggest that m^{6}A modification of peripheral blood can be used as a new non-invasive biomarker for GC prediction and diagnosis [61]. Moreover, He et al., demonstrated that m^{6}A modification plays a regulatory role in miR-660-mediated inhibition of GC cells, providing a novel perspective for the m^{6}A regulatory mechanism in GC development [62].

However, Zhang et al., obtained contradictory results and found that the m^{6}A methyltransferases are potential tumor suppressors, while demethylases are potential cancer promoters. Further studies revealed that METTL14 knockdown could promote the proliferation and invasion of GC cells by activating the oncogenic Wnt/PI3K-AKT signaling, while FTO knockdown exhibits the opposite effects [63]. These results indicate that the molecular mechanism of m^{6}A involved in the occurrence and development of GC is still complicated and worthy of further exploration.

Breast cancer (BC)

Breast cancer (BC) is the most common cause of death among women in the world. Although early treatment of BC is effective, 30% of patients still face the risk of tumor recurrence or metastasis [64, 65]. Under hypoxic conditions in the tumor microenvironment, the expression of ALKBH5 in Breast cancer stem cells (BCSCs) is increased, which reduces the m^6A methylation levels in tumor tissues and ultimately promotes the enrichment of BCSCs in the hypoxic microenvironment. Mechanistically, ALKBH5 reduces the m^6A methylation level of NANOG, a totipotent or pluripotent stem cell transcription factor, to upregulate its mRNA stability [66, 67]. Furthermore, hypoxia can also induce expression of zinc finger protein 217 (ZNF217) in BC cells in a HIF-dependent manner. As an inhibitor of m^6A methyltransferase, ZNF217 reduces METTL3 but upregulates ALKBH5 level to negatively regulate m^6A levels of downstream genes, resulting in promoting BC tumorigenesis by increasing expression of KLF4 and NANOG [68].

As a pro-apoptotic gene, BNIP3 is a tumor suppressor in BC. In BC, the expression of FTO is upregulated. FTO targets BNIP3 and mediates its mRNA demethylation, which induce degradation of *BNIP3* mRNA in YTHDF2-dependent manner, resulting in BC cell proliferation, metastasis and colony formation [69].

The methyltransferase METTL3 is highly expressed in BC, and has a strong positive correlation with expression of oncoprotein hepatitis B virus x-interacting protein (HBXIP) in tumor development. Moreover, METTL3 increases HBXIP expression through methylation modification, and HBXIP in turn promotes the expression of METTL3 by inhibiting the METTL3 inhibitor miRNA let-7 g expression. These results identify that HBXIP/let-7 g/METTL3/HBXIP forms a positive feedback pathway, accelerating the development of BC [70]. Furthermore, Wang et al., found that METTL3 targets Bcl-2 and increases its transcription, thereby inhibiting cell apoptosis and promoting the progress of BC [71]. Collectively, these results provide new potential therapeutic targets for BC.

Non-small-cell lung carcinoma (NSCLC)

In China, lung cancer is one of the malignant tumors with the highest morbidity and mortality, and it is the greatest threat to the health and life of the population [72, 73]. According to histopathological criteria, lung cancer can be divided into small-cell lung carcinoma (SCLC) and NSCLC, among which common non-small-cell carcinomas include lung adenocarcinoma (LUAD) and squamous cell carcinoma. Lin et al., found that METTL3 mRNA levels in LUAD are significantly increased; further studies identified that METTL3 regulates LUAD growth and invasion [28]. Moreover, other studies revealed that METTL3 induces brain metastasis of lung cancer by regulating expression of miR-143-3p and vascular tissue protein 1 (vasohibin-1, VASH1) [74]. METTL3 also participates in the Transforming Growth Factor-beta (TGF-β)-mediated EMT process of lung cancer cells via modulating the expression of JUNB, a key transcriptional regulator of EMT [75]. In another study on NSCLC, miR-33a was observed to directly binds to the 3′ non-coding region of METTL3 mRNA to reduce the expression of METTL3, which in turn inhibits cancer cell proliferation by decreasing the expression of target genes EGFR, TAZ and DNMT3A [76]. These results suggest that METTL3 may become one of the targets of lung cancer treatment.

Liu et al., confirmed that FTO promotes the progression of lung squamous cell carcinoma via reducing the m^6A methylation level of zinc finger 1 (MZF1) and in turn enhancing its protein levels [77, 78]. Li et al., also found that FTO can accelerate the growth of lung cancer cells by targeting the m^6A level of ubiquitin-specific protease 7 (USP7) [79].

Other tumors

m^6A has been found to be involved in the occurrence and development of human urinary system-related tumors in recent studies including renal cell carcinoma (RCC), bladder cancer (BCA), and male prostate cancer (PCA) [80–86]. RCC is the most fatal malignant tumor of the urinary system [58], in which METTL3 can inhibit the proliferation, migration and epithelial-mesenchymal transition of renal cancer cells by regulating the PI3K-AKT-mTOR pathway [80]. Methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), overexpressed in RCC, can enhance the m^6A modification of hypoxia-inducible factor-2α (HIF-2α) and thus induce translation of HIF-2α, promoting glycolytic metabolism in tumor cells and malignant phenotype of tumors [81]. In BCA, METTL3 with increased expression upregulates the methylation level of CUB domain-containing protein 1 (CUB domain-containing protein 1, CDCP1), and YTHDF1 then recognizes the m^6A motifs in CDCP1 3'-UTR to facilitate translation of the oncogene CDCP1 [82]. Recent studies have demonstrated that the METTL3-YTHDF2 axis can directly target and recognize the downstream tumor suppressor genes SETD7 and KLF4 mRNA to induce their degradation, thereby promoting the pathogenesis and development of BCA [83]. In addition, Gao et al. revealed the METTL3-AFF4-SOX2/MYC regulatory axis plays a key role in the self-renewal and tumorigenicity of BCA stem cells [84]. In PCA, YTHDF2 and miR-493-3p are confirmed to be two key oncogenes to participate in the progression of PCA [85]. Ma et al. found that METTL3 increases m^6A methylation levels of LEF1 mRNA, increasing its protein translation and

enhancing the activity of the Wnt signaling pathway to promote the occurrence and development of PCA [86].

Among gynecological tumors, m^6A is involved in cervical squamous cell carcinoma (CSCC), ovarian cancer (OC), and endometrial cancer (EC) [87–89]. In CSCC, Zhou et al., found that FTO reduces β-catenin expression by reducing the m^6A levels in its mRNA transcripts, thereby increasing the excision repair cross-complementation group 1 (ERCC1) activity to enhance the resistance of CSCC to chemotherapy and radiotherapy [87]. Moreover, YTHDF1 increases the translation of EIF3C by recognizing the m^6A modification sites in EIF3C mRNA, and elevated EIF3C ultimately promotes the progression of OC [88]. In EC, Liu et al., demonstrated that estrogen decreases the m^6A methylation levels by downregulating the METTL3/METTL14 levels in cancer cells, which then reduces the expression of the negative AKT regulator PHLPP2, but induces the expression of the positive regulator mTORC2, thereby activating the AKT signaling pathway and enhancing cancer cell proliferation, migration, and invasion [89].

In uveal melanoma (UM), METTL3-mediated m^6A methylation modification regulates the proliferation, migration and invasion of UM cells by targeting c-Met. As a protein product encoded by the proto-oncogene c-Met, c-Met plays a critical carcinogenic role in the development of UM [90]. Moreover, METTL3 can promote cancer cell proliferation and tumor growth in cutaneous squamous cell carcinoma (cSCC) by upregulating the expression of delta Np63, one of the subtypes of p63 gene, which plays an important role in the growth, differentiation and pathological development of normal epithelium [91].

The dual role of m^6A in tumorigenesis and development

We have found that although m^6A modification plays a broad role in the occurrence and development of various tumors, and the mechanisms are diverse and complex (Table 1 and Fig. 2). In many types of cancer cells, increased m^6A levels are associated with upregulated expression of oncogenes, decrease apoptosis of cancer cells, and improved cellular migration and invasion abilities, which are conducive to the cancer progression. Moreover, the increased m^6A levels could improve resistance of cancer cells to drugs and shorten life expectancy of patients. For example, Hua et al. found the upregulated METTL3 promotes the occurrence and invasion of OC by stimulating AXL transcription and inducing EMT progression [92]. However, in the research on colorectal cancer (CRC), the effects of m^6A on tumors are diverse and contradictory. Li et al., found that METTL3 improves the stability of SOX2 mRNA and increases the expression of SOX2 through m^6A-IGF2BP2-dependent mechanism in CRC, which enhances the stemness of CRC cells and finally promotes cancer progression [93]. Similarly, Wen et al., confirmed that METTL3 promotes CRC metastasis via miR-1246/SPRED2/MAPK signaling pathway [94]. However, Deng et al., found that METTL3 inhibits the proliferation and migration of CRC through the p38/ERK pathway [95]. The contradictory effects of m^6A are also reflected in the researches on glioblastoma [39–42]. In addition, different studies have found that at different stages of liver cancer development, METTL3 and ALKBH5 promote the progression of HCC by up-regulating or down-regulating the m^6A modification levels [48, 50], which may provide new insights into understanding the roles of m^6A in regulating cancer.

Drugs and targeted therapies in cancer development

In the research of targeted therapeutics against m6A for tumors, the research on FTO targeted therapies is the most accomplished and representative. Since Han et al. discovered the crystal structure of FTO in 2010, the research on FTO inhibitors has gained more and more attention [96]. Up to date, various small molecules have been applied to inhibit FTO expression, such as Rhein [97], meclofenamic acid [98], R-2HG [99], entacapone [100], etc. However, due to the low sensitivity and specificity, the potential for clinical application of these FTO inhibitors are limited [101]. Huang et al. recently discovered two derivatives of meclofenamic acid, FB23 and FB23-2, which could remarkably reduce the survival rate of AML cells and show the potential to treat AML [102]. Su et al. also found two new high-efficiency FTO inhibitors CS1 and CS2, which show strong anti-leukemia effects in vitro [101]. Yang et al., revealed that knocking out the FTO gene could reduce the resistance of melanoma to anti-PD-1 immunotherapy [103]. In summary, the main effects of FTO inhibitors against tumors include reducing tumor cell drug resistance, inhibiting cancer stem cell proliferation and suppressing immune evasion, suggesting the possibility of FTO as a promising therapeutic target.

In addition to FTO, many studies on other m6A-related enzymes for targeted therapy of tumors have been performed in recent years. Wang et al., reported that knocking out METL3 or METL14 can enhance the responsiveness of colorectal cancer and melanoma cells to immunotherapy by regulating the IFN-γ-Stat1-Irf1 signaling [104], and Li et al., succeeded in using ALKBH5 specific inhibitor ALK-04 to improve the efficacy of immunotherapy for colorectal cancer and melanoma [105]. It is noted that Bedi RK et al., proposed potent and selective inhibitors of METTL3, which is conducive to developing target drugs [106].

In short, although the current targeted therapeutics against m6A for treating cancer is still in its infancy, it is promising to develop clinically effective drugs in the near

Table 1 Functional roles of m^6A modification in cancer progression

Cancers	m^6A effectors	Promote or Suppress cancer	Mechanism	References
Acute myeloid leukemia (AML)	METTL3	Promote	Promote the expression of c-MYC, BCL-2 and PTEN in AML cells	[30]
		Promote	Upregulate the m6A methylation levels on the oncogenes SP1 and SP2 mRNAs	[32]
	METTL14	Promote	The SP1-METTL14–MYB/ MYC signal axis can inhibit the myeloid differentiation of normal cells and participate in malignant hematopoiesis	[31]
	ALKBH5	Promote	Function as an oncoprotein	[35]
Glioblastoma (GBM)	METTL3	Promote	Upregulate SOX2 expression	[40]
		Promote	Function as a regulator of NMD to maintain the aggressiveness of tumor	[41]
		Suppress	Downregulate the expression of oncogenes, such as ADAM19, EPHA3, and KLF4	[39]
	ALKBH5	Promote	Promote the expression of the oncogene FOXM1	[43]
	IGF2BP2	Promote	Upregulate IGF2 and then activate PI3K/AKT signaling pathway	[44]
Hepatocellular carcinoma (HCC)	METTL3	Promote	Reduce the mRNA stability of the tumor suppressor SOCS2	[47]
		Promote	Enhance the translation of Snail protein alone with YTHDF1	[48]
	METTL14	Promote	Mediate the recognition and binding of DGCR 8to pri-miR-126, resulting in miR-126 maturation	[50]
	WTAP	Promote	Modulate the G2/M phase of HCC cells through a p21/p27-dependent pattern mediated by ETS1	[53]
	KIAA1429	Promote	Induce m6A methylation on the 3' UTR of GATA3 pre-mRNA	[54]
	FTO	Promote	Trigger the demethylation of PKM2 mRNA and accelerated the translated production	[55]
	ALKBH5	Suppress	Decrease the m6A methylation modification of LYPD1	[57]
Gastric cancer (GC)	METTL3	Promote	Increase the m6A modification levels of HDGF mRNA	[59]
	ALKBH5	Promote	Reduce m6A modification levels of the lncRNA NEAT1	[60]
Breast cancer (BC)	METTL3	Promote	HBXIP/let-7 g/METTL3/HBXIP forms a positive feedback pathway, accelerating the development of cancer	[70]
		Promote	Target Bcl-2 and increases its transcription	[71]
	ALKBH5	Promote	Target NANOG and downregulate the m6A methylation level of its mRNA, upregulating the mRNA stability	[67]
	FTO	Promote	Target BNIP3 and mediates its mRNA demethylation	[69]
Non-small-cell lung carcinoma (NSCLC)	METTL3	Promote	Regulate expression of miR-143-3p and vascular tissue protein 1, inducing brain metastasis	[74]
		Promote	Modulate the expression of JUNB, participating in EMT process of lung cancer cells	[75]
	FTO	Promote	Reduce the m^6A methylation level of MZF1, enhancing its protein levels	[77]

Table 1 (continued)

Cancers	m^6A effectors	Promote or Suppress cancer	Mechanism	References
Renal cell carcinoma (RCC)	METTL3	Suppress	Regulate the PI3K-AKT-mTOR pathway	[80]
	MTHFD2	Promote	Enhance the m^6A modification of HIF-2α and induce translation of HIF-2α	[81]
Bladder cancer (BCA)	METTL3	Promote	METTL3-YTHDF1 axis targets and upregulates the methylation level of the oncogene CDCP1	[82]
		Promote	METTL3-YTHDF2 axis targets and recognize the downstream tumor suppressor genes SETD7 and KLF4 mRNA	[83]
Prostate cancer (PCA)	METTL3	Promote	Act on LEF1 mRNA through m^6A methylation and enhance the activity of the Wnt signaling pathway	[86]
Ovarian cancer (OC)	YTHDF1	Promote	Recognize the m^6A modification sites in EIF3C mRNA, increasing the translation of EIF3C	[88]
Endometrial cancer (EC)	METTL3/METTL14	Suppress	Induce the expression of PHLPP2 and reduce the expression of mTORC2	[89]
Uveal melanoma (UM)	METTL3	Promote	Target c-Met	[90]
Cutaneous squamous cell carcinoma (cSCC)	METTL3	Promote	Upregulate the expression of delta Np63	[91]

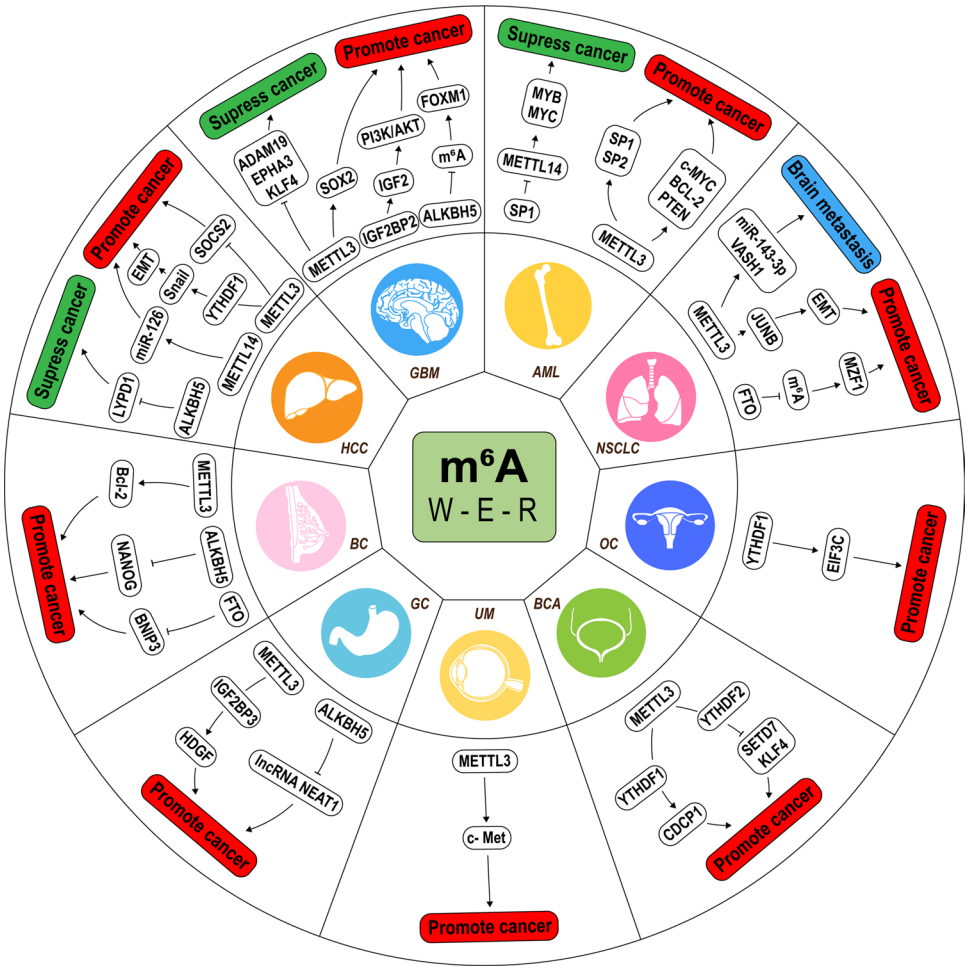

Fig. 2 Functional roles of m^6A in development of various cancers. The m^6A modification exerts diverse effects on various cancers. *AML* acute myeloid leukemia, *GBM* glioblastoma, *HCC* hepatocellular carcinoma, *GC* gastric cancer, *BC* breast cancer, *NSCLC* non-small-cell lung carcinoma, *BCA* bladder cancer, *OC* ovarian cancer, *UM* uveal melanoma, *W-E-R* writers, erasers, readers

future with the increasing knowledge of related molecular mechanisms of m6A modification being explored.

Conclusion and perspectives

This review summarizes the different roles of m^6A modification and the underlying mechanism in cancer development, and reveals that m^6A modification plays a critical role in the occurrence and development of various cancers. But our knowledge about m^6A is far from complete, and current research results on m^6A cannot provide accurate and universal guidance for the clinical diagnosis and therapeutic strategies of cancer yet. Little is known about whether the regulation of tumors by m^6A-related proteins is associated with tumor types and tumor progression stages, whether the inhibition of m^6A regulatory factors for a certain tumor leads to the occurrence of another tumor or other diseases. The challenges need to be explored and solved urgently. Under these circumstances, clearer research directions have emerged: the first is to clarify the phenotype, staging and prognosis of m^6A-related cancers; the second is an anti-tumor therapy research related to m^6A; the third is a new immunotherapy strategy targeting m^6A [107].

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Declarations

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