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Review Article

N6-methyladenine RNA modification and cancers

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Abstract: Similar to DNA methylation modifications, N6-methyladenine (m^6A) has been identified as a dynamic and reversible modification in messenger RNA (mRNA), regulated by m^6A methyltransferases and demethylases. m^6A modifications regulate gene expressions and play vital roles in many life processes. Some proteins serve as m^6A-binding proteins to perform the m^6A-modified biological functions. Recently, m^6A modifications have been reported to play critical roles in human cancers, including lung cancer, brain tumor, leukemia, and many others. In this comprehensive review, we have described the roles played by m^6A modifications of mRNA in the development of cancers. These modifications appear to have an oncogenic role in some cancers while a tumor-suppressor role in others. Therefore, it would be of great significance to study the biological functions of genes regulated by m^6A in different cancers and identify the key m^6A target genes to understand the potential mechanism underlying the pathogenesis of cancer.

Keywords: RNA epigenetics, N6-methyladenine (m^6A), methyltransferases, demethylases, cancer

Introduction

Epigenetics is the study of reversible and heritable phenotypic changes that do not involve changes in nuclear DNA sequences [1]. It includes DNA and RNA methylation, histone modifications, non-coding RNA modification, and chromatin rearrangement. These dynamic modifications affect critical biological processes like gene expression and protein function, and play important regulatory roles in biological growth and development, senescence, disease occurrence, and so on. Among the epigenetic modifications, DNA methylation and histone modifications are well studied. 5-Methylcytosine methylation in DNA has been shown to extensively affect gene expression in many diseases such as cancer [2]. Histone methylation, acetylation, phosphorylation, and ubiquitination also play important roles in regulating gene expression and maintaining chromosome structure [3]. Emergence of new targets, such as demethylation drugs decitabine and azacitidine, and histone deacetylase inhibitor cedaramine, has provided more strategies for treatment of clinical diseases [4, 5].

Similar to epigenetic DNA modifications, more than one hundred types of RNA modifications have been discovered [6]. These RNA modifications ubiquitously occur in eukaryotic species and substantially enrich the functions of RNA and diversity of genetic information [7]. RNA methylation, the main form of RNA modification, widely exists in various types of RNAs, such as ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), some small nucleolar RNA (snoRNA), and mRNA. As a core molecular connection between DNA and proteins, mRNA is part of the genetic information reading process, and its chemical modification is, therefore, most widely studied. Modifications of mRNA include N7-methylguanine (m^7G), N6-methyladenine (m^6A), 5-methylcytosine (m^5C), N1-methyladenine (m^1A), and 2'-O- Methylation modification (Nm). Among them, m^6A modification accounts for approximately 80% of mRNA modifications, justifying the extensive attention and research in the recent years.

N6-methyladenine (m^6A)

Methylation on the sixth atom of the base, also known as m^6A RNA modification, is highly conserved, and extensively occurs in most eukaryotic species (from yeast, plants, and fruit flies to mammals) as well as in viral mRNA, and plays critical regulatory roles in post-transcriptional

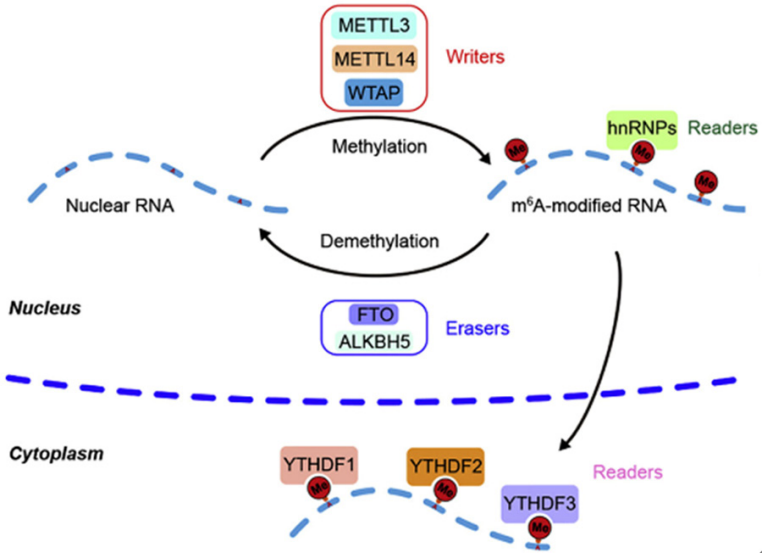

Figure 1. Cellular pathways of m^{6}A-based modification of RNA. m^{6}A methyltransferase complex METTL3-METTL14-WTAP and m^{6}A demethylases FTO and ALKBH5 dynamically and reversibly regulate the m^{6}A levels in RNA within the nucleus. Nuclear m^{6}A-reader proteins (hnRNPs) affect alternative splicing of pre-mRNA and pre-microRNA. Cytoplasmic m^{6}A-reader proteins (YTHDF1/2/3) are engaged in decay and translation of m^{6}A-containing mRNAs [15]. This figure is adapted from **Figure 1** of the paper by Siwei Wang et al. [15].

mRNA processing and metabolism [8]. Despite its discovery in the 1970s by Desrosiers et al., the function of m^{6}A RNA methylation remains largely unknown [9]. It was not until 2011, after the identification of fat mass and obesity-associated protein (FTO) as m^{6}A mRNA demethylase and establishment of m^{6}A as a reversible modification, that the research on m^{6}A modification became popular [10]. In 2012, two research teams independently reported high throughput sequencing of m^{6}A at the whole transcriptome level. The m^{6}A antibody affinity enrichment, combined with high-throughput sequencing method m^{6}A-seq and Methylated RNA Immunoprecipitation sequencing (MeRIP-seq), established a substantial technical foundation for research on m^{6}A [11, 12]. Since then, significant progress has been made and several important proteins including methyltransferase complex (writer) of methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and Wilms' tumor 1-associated protein (WTAP), two m^{6}A demethylases (eraser) FTO and ALKBH5 [10, 13], and several m^{6}A-binding proteins (reader) including YT521-B homology (YTH) domain family of proteins and heterogeneous nuclear ribonucleoproteins A2/B1 (HNRNPA2B1) have been identified [14]. Together, these achievements have helped elucidate the fundamental process of m^{6}A modification in RNA-methyltransferase complex of METTL3, METTL14, and WTAP that catalyzes the formation of m^{6}A in mRNA, which can be subsequently de-methylated by the two m^{6}A demethylases FTO and alkB homolog 5 (ALKBH5); the m^{6}A-binding protein of YTH domain family and nuclear HNRNPA2B1 bind to the sequences modified by m^{6}A RNA methylation and perform the m^{6}A-modified biological functions. Analogous to chemical modifications in DNA and histone, m^{6}A modification in RNA is also regulated dynamically and reversibly by both methyltransferases and demethylases with respect to time and space. The dynamic and reversible process of m^{6}A modification is presented in **Figure 1** [15].

In 2012, Dominissini and Meyer's groups reported m^{6}A modification spectrum at the transcriptional level through high-throughput m^{6}A-seq in human and mouse respectively [11, 12]. They identified more than 12,000 m^{6}A modification sites, distributed in 7,000 coding gene transcripts and 300 non-coding gene transcripts or non-coding RNA (ncRNA). m^{6}A was enriched around protein coding sequence (CDS), 3'-untranslated regions (3'-UTR), stop codons, near splice sites and long exon regions, as well as microRNA target sites and mRNA adjacent regions. All the modified regions harbored a consensus sequence "RRACH" ([G>A]m^{6}AC[U>A>C]). Modification spectrum of m^{6}A is highly conserved between human and mouse, prominently concentrated in the human brain, heart, and kidney, and is tissue-specific.

As a representative of the epitranscriptome, m^{6}A mRNA modifications participate in many vital activities in the cell, including stem cell self-renewal and differentiation, mRNA transcription, alternative splicing, nuclear export, translation, degradation, and microRNA processing. These processes determine the expression or inactivation of specific genes, which is vital for growth and development. Dominissini

et al. [11] reported that silencing of m^{6}A methyltransferases increases gene expression levels and patterns of alternative splicing, and affects p53-signaling pathway and apoptosis. Batista confirmed that m^{6}A can promote the transformation of a stem cell from a self-renewal phenotype to a differentiating phenotype [16]. Knockdown of METTL3 or WTAP in zebrafish led to multiple defects in early development and promoted apoptosis [17]. m^{6}A could dynamically alter the secondary structure of mRNA and regulate mRNA-protein interactions affecting the alternative splicing of mRNA [18, 19]. Chen et al. found that microRNAs regulate the binding of METTL3 to mRNA through sequence-matching mechanisms and affect the formation of m^{6}A. Their study also revealed that over-expression of METTL3 causes a significant increase in m^{6}A levels which further increases the efficiency of mouse fibroblast reprogramming into pluripotent stem cells. Treatment with cycloleucine, a small-molecule inhibitor of m^{6}A, inhibited reprogramming and showed similar effects as METTL3 knockdown [20]. Alarcon et al. revealed that HNRNPA2B1 could identify and bind to m^{6}A on the pre-microRNA transcripts and participate in microRNA splicing processes [21]. Wang et al. found that m^{6}A could control the translation efficiency of mRNA through its binding protein YTHDF1 [14]. Additionally, Xiao et al. had uncovered that YTHDC1 interacts with SRSF3 to control mRNA splicing [22].

In brief, similar to DNA and histone modifications, m^{6}A is a novel epigenetic RNA modification, which regulates gene expression and is vital in many life processes.

m^{6}A methyltransferase complex and cancers

METTL3, METTL14, and cancers

m^{6}A methyltransferase complex utilizes S-adenosyl methionine (SAM) as a methyl group donor to methylate the hydrogen on N center at position 6 of adenine. METTL3 has two binding sites for SAM and catalyzes m^{6}A synthesis [23]. Immunofluorescence analysis showed that METTL3 is mainly distributed in the nuclear speckle, the main site of RNA processing, hence indicating that m^{6}A plays a prominent regulatory role in RNA processing [17]. METTL3 is highly abundant in human tissues, especially in the testes, and is conserved across multiple species. Knockdown of METTL3 leads to apoptosis and decrease in m^{6}A levels in HeLa cells and HepG2 cells [11]. In 2014, Liu et al. reported that METTL14 also possesses SAM-binding sites, along with an active site of EPPL, to catalyze m^{6}A synthesis [24]. Therefore, MELLT14 was considered as another subunit of the m^{6}A methyltransferase complex. During m^{6}A synthesis, METTL14 and METTL3 form a stable heterodimer in the ratio of 1:1. The heterodimer is characterized by high enzyme activity and strong substrate preference. Consistent with the conserved sequence of m^{6}A, the heterodimer preferentially methylates the GGACU locus without strict requirements of the secondary structure of RNA substrate. Depletion of METTL14 could lead to m^{6}A reduction in mRNA of both HeLa and HEK93 cells.

With the development of RNA epigenetics, the relation between METTL3, METTL14, and tumors has gradually become a hot research topic. In recent years, METTL3 and METTL14 have been reported to play an important role in cancer, including lung cancer, brain tumor, leukemia, and others. In 2016, Lin and his team detected 9298 m^{6}A peaks on target genes in the lung cancer cell line A549, using meRIP-seq technology. m^{6}A on the oncogenes of EGFR, TAZ, and DNMT3A are mainly distributed around the stop codon, but m^{6}A on the c-MYC gene is diffusely distributed in multiple exons. METTL3 knockdown leads to down-regulation of EGFR, TAZ, and DNMT3A genes, but not of c-MYC. METLL3 promotes the translation of mRNA oncogenes with abundant m^{6}A, by interacting with the translation initiation complex eIF3b in the cytoplasm. Increasing the expression of METTL3 could promote proliferation, growth, and invasion of lung cancer cells [25]. In 2017, Du et al. reported that the expression of METTL3 in non-small cell lung cancer (NSCLC) tissues were higher than that in paracancerous tissues. The expression of METTL3 in NSCLC tissues was positively correlated with that of miR-33a. MiR-33a is able to reduce METTL3 expression at both mRNA and protein levels, revealing a new mechanism of METTL3 regulation by miRNA [26]. Cui et al. reported that knockdown of METTL3 or METTL14 evidently enhanced stem cell growth and self-renewal capability of glioblastoma cells to promote the development of tumors, whereas over-expression of METTL3 had an opposite

effect. They also reported that ADAM19 may be a target gene of m6A [27]. The roles possibly played by m6A in leukemia have also been significantly identified. Vu and his team revealed, from three patients with AML, that METTL3 is highly expressed in acute myeloid leukemia (AML) cells and primary leukemia cells. After knockdown of METTL3 by shRNA, the m6A levels in AML cells decreased with increase in differentiation and apoptosis and decrease in colony formation capacity. m6A individual-nucleotide-resolution cross-linking and immunoprecipitation (miCLIP) and RNA-seq analyses showed that METTL3 improved m6A levels of mRNA in the target genes C-MYC and BCL2, and enhanced its translation by stabilizing the mRNA, hence resulting in higher expression of target genes while retaining the AML cells in undifferentiated state [28]. Weng et al. discovered that mRNA of METTL14 was enriched in normal hematopoietic stem/progenitor cells (HSPCs) and AML leukemia cells including t(11q23), t(15;17), and t(8;21), and was downregulated after cell differentiation. Knockdown of METTL14 could promote the differentiation of normal HSPCs and AML cells, but inhibit proliferation of the latter. Further, mechanistic studies have shown that METTL14 influences the expression of target genes, sustains leukemia stem/initiation cells (LSCS/LICs) and their self-renewal, and enforces the development of leukemia by regulating the levels of m6A in the mRNA of MYB, MYC, and other target genes [29]. Thus, METTL14 is required for both leukemogenesis and maintenance of leukemia stem/initiation cells; it acts as a proto-oncogene via m6A modification in the mRNA of targets.

m6A expression was decreased in hepatocellular carcinoma tissues compared to that in adjacent non-neoplastic and normal tissues. Downregulation of METTL14 had poor prognosis in patients with HCC. METTL14 mRNA expression was found to be very low in metastatic tumors or portal vein tumor thrombus, indicating the inhibition of hepatoma cell metastasis by METTL14. Co-immunoprecipitation assay demonstrated that forced expression of METTL14 resulted in increased levels of mature miR126 and pri-miR126 binding to DGCR8, thereby suggesting that METTL14 suppresses HCC metastasis by increasing miR126 level in an m6A-dependent manner. Recent studies showed that depletion of m6A levels by knock-down of METTL3/METTL14 using shRNA, or over-expressing FTO/ALKBH5, in cervical cancer cell line SiHa augmented tumor growth. Conversely, elevated levels of m6A restrain the growth of cervical cancer cells, hence suggesting a tumor-suppressor role of METTL3 and METTL14 in cervical cancer [30]. Investigations of renal cell carcinoma revealed that high expression of METTL3 in patients with renal cell carcinoma indicated good prognosis, which implies that METTL3 may act as a tumor-suppressor gene in the process of cell proliferation, aggressiveness, and metastasis in renal cell carcinoma. METTL3 might be acting via the regulation of epithelial-to-mesenchymal transition, and PI3K-Akt-mTOR pathways [31]. Taken together, METTL3 and METTL14 have an oncogenic role in lung cancer as well as in acute myeloid leukemia, and a tumor-suppressor role in glioblastoma, hepatocellular carcinoma, cervical cancer, and renal cancer.

WTAP and cancers

Initially recognized as a splicing factor binding to Wilms' tumor 1 (WT1) protein, WTAP has been subsequently reported to be a component of m6A methyltransferase complex. It regulates m6A modification by forming a trimer with METTL3 and METTL14. WTAP has no methyltransferase activity, and its interaction with the METTL3-METTL14 heterodimer is relatively weaker than that between METTL3 and METTL14 [24]. Similar to METTL3 and METTL14, WTAP localizes in the nuclear speckle. WTAP, as a cofactor, binds to the target mRNA in the nuclear speckle, and recruits the catalytic subunit of METTL3-METTL14 heterodimer. This composes a new complex that governs the binding of METTL3-METTL14 heterodimer to their target mRNA, and accelerates the synthesis of m6A. Knockdown of WTAP can prevent METTL3 from localizing to the nuclear speckle, thereby subsequently resulting in decreased m6A levels [18, 28, 32].

Previous studies had suggested that more than 30% patients with AML have WTAP overexpression, which is associated with FLT3-ITD and NPM1 mutation [33]. Absence of WTAP can restrain AML cell proliferation, survival, and tumor growth while the mechanism related to m6A remains to be clarified. WTAP was reported to combine with cell cycle-dependent kinase 2

(CDK2) to strengthen its transcription activity and promote cancer growth, probably playing oncogenic roles in renal cancer, without involving m6A [34]. As a cofactor for METTL3 and METTL14, WTAP is believed to regulate the development and growth of tumor through m6A.

m6A demethylases and cancers

Discovery of m6A demethylases has strongly demonstrated that m6A modification is dynamic and reversible. m6A demethylases FTO [10] and ALKBH5 [13] can catalyze m6A demethylation in α-ketoglutarate- and Fe(II)-dependent manner. Recently, FTO and ALKBH5 were reported to play a critical role in many biological processes, including biological development, metabolism, and reproduction. FTO was first known to be located in the nucleus and robustly implicated in increased body mass and body mass index in humans. In 2011, FTO was found to govern the level of m6A both *in vivo* and *in vitro* [10]. Another demethylase ALKBH5 is expressed in most tissues, particularly abundant in the testes. Like FTO, ALKBH5 is enriched in the nuclear speckles, and its loss noticeably influences RNA metabolism and mRNA assembly in the nuclear speckles. Although ALKBH5 depletion in mice does not affect growth and physiology, fertility is impaired due to apoptosis of spermatocyte in the mid-meiosis stage [13].

Recently, FTO was reported to be highly expressed in AMLs with MLL-rearrangement, FLT3-ITD, and/or NPM1 mutations; depletion of FTO was shown to inhibit cell growth in MLL-rearranged AML [35]. Comparing the over-expression of mutated FTO (H231A and D233A) in MLL-rearranged AML cells, only over-expression of the wild-type FTO was found to promote leukemia cell growth. Upon FTO knockdown, the level of m6A was up-regulated, demonstrating that FTO regulates this phenotype by regulating m6A modifications. The phenotype appeared in AMLs with PML-RARA and FLT-ITD/NPM1 mutations as well. Experiments with bone marrow transplantation assay implied that over-expression of FTO can accelerate leukemogenesis induced by MLL-AF9. The study showed that mRNA of SOCS box-containing 2 (ASB2) and retinoic acid receptor-α (RAR α) were down-regulated due to the hypomethylated m6A peak in AML cells after over-expression of FTO. The two proteins were up-regulated in all-trans retinoic acid (ATRA)-induced differentiation of leukemia cells [36, 37]. Further studies demonstrated that FTO blocks ATRA-induced AML cell differentiation by governing the transcription of ASB2 and RARA, thereby indicating a critical oncogenic role of FTO in leukemogenesis.

The poor prognosis of glioblastoma (GSCs) had earlier been correlated with ALKBH5 over-expression [38]. Silencing of ALKBH5 suppressed the proliferation of GSCs, which could be rescued with wild-type ALKBH5. Mutated ALKBH5 (H204A) that lacked catalytic activity could not rescue cell proliferation. Integrating m6A IP-seq and transcriptomic analyses of GSC with ALKBH5 knockdown established forkhead box M1 (FOXM1) as a vital target gene of ALKBH5. High expression of FOXM1, a key protein of cell cycle, has been reported to be associated with poor prognosis of malignant gliomas. Decrease of m6A levels, secondary to the abundant presence of ALKBH5, enhances the connection between Human antigen R (HUR) and pre-mRNA of FOXM1, which subsequently increases the stability of FOXM1 pre-mRNA49. Additionally, lncRNA FOXM1-AS strengthens HUR binding by promoting the interaction between ALKBH5 and nascent transcripts of FOXM1. Loss of ALKBH5 and FOXM1-AS-induced FOXM1 over-expression and inhibited GSC growth further verified that FOXM1 plays a key role in GSC tumorigenesis [38]. Hypoxia in breast cancer stem cells (BCSCs) results in the high expression of ALKBH5 with reduction of m6A levels in a HIF-dependent manner [39]. This demethylation enhances the stabilization of NANOG mRNA and leads to NANOG up-regulation. While depletion of ALKBH5 impaired BCSC enrichment induced by hypoxia, over-expression of ALKBH5 clearly implied hypoxia. Therefore, HIF-dependent ALKBH5 expression aided BCSC enrichment in the hypoxic tumor microenvironment [39]. In addition, METTL14 level distinctly decreased in patients with breast cancer, and was strongly associated with a shorter survival time [35].

m6A-binding proteins and cancers

He et al. (2013) reported YTHDF2 as a reader of m6A. YTHDF2 affects the stabilization of RNA by identifying and binding to the m6A sites of target RNA [7]. Three proteins YTHDF1/2/3 have been identified as the selective

Table 1. Potential role of m^{6}A regulators in different cancers

Cancer	m^{6}A regulators	Related genes	Potential Role	Ref.
AML	METTLE3	C-MYC and BCL2	Oncogene	[28]
	METTLE14	MYB, MYC	Oncogene	[29]
	WTAP	N	Oncogene	[33]
Cervical cancer	METTL3/METTL14	N	Tumor-suppressor	[30]
	FTO/ALKBH5	N	Oncogene	[30]
Breast cancer	ALKBH5	NANOG	Oncogene	[39]
Colorectal cancer	YTHDF1	Associated with c-Myc	Oncogene	[52]
Glioblastoma	METTL3/METTL14	ADAM19	Tumor-suppressor	[27]
	ALKBH5	FOXM1	Oncogene	[38]
HCC	METTLE14	miR126	Tumor-suppressor	[34]
	YTHDF2	Associated with miR-145	Oncogene	[53]
Lung cancer	METTLE3	EGFR, TAZ, DNMT3A	Oncogene	[25]
MLL-rearranged AML	FTO	ASB2, RARA	Oncogene	[36, 37]
Renal cell carcinoma	METTL3	PI3K-Akt-mTOR pathways	Tumor-suppressor	[31]
	WTAP	Associated with CDK2	Oncogene	[34]

Note: N means there are no known relevant genes in this review.

binding proteins of m^{6}A in mammals. All three harbor a relatively conserved carboxy-terminal YTH domain for binding to m^{6}A, as well as a more variable amino-terminal effector domain. YTHDF2 selectively binds to m^{6}A-modified mRNA, recruits them to mRNA degradation sites, controls their stability [7], and promotes mRNA degradation through CCR4-NOT-mediated demethylation [40]. YTHDF1 interacts with the translation initiation factor to enhance target RNA translation [14]. The cooperation between YTHDF3 and YTHDF1 promotes translation and YTHDF2-induced degradation of mRNA [41, 42]. The three proteins YTHDF1/2/3, thereby, coordinate to regulate the metabolism of RNA. YTH (YT521-B homology) domain-containing protein 1 (YTH domain containing 1, YTHDC1) is a nuclear m^{6}A-binding protein that regulates splicing [43, 44]. Heterogeneous nuclear ribonucleoproteins A2/B1 (HNRNPA2B1) bind m^{6}A-modified transcription factors and regulate splicing and maturation of microRNA (miRNA) in the nucleus [21]. Furthermore, m^{6}A has been shown to influence the secondary structure of RNA and regulate RNA-binding capability of RNA-binding proteins (RBP) in the adjacent region of m^{6}A. This mechanism, known as an "m^{6}A switch", promotes the binding of HNRNPC and HNRNPG to target genes and controls the abundance and splicing of mRNA [44-48].

In gynecologic tumor cell lines, reduction of YTHDC1 protein levels, owing to hypoxia, alters RNA splicing [49]. It was showed that m^{6}A-binding protein YTHDF2 enhances translation of HIF-α and HIF-1 and results in metastasis of colon tumors [50, 51]. These studies have revealed how the tumor microenvironment influences gene expression by epi-transcriptomes leading to devastating outcomes. On the other hand, research has shown that oncogene c-Myc promotes the expression of m^{6}A-binding protein YTHDF1 in colorectal cancer while its knockdown inhibits YTHDF1 expression [52], therefore indicating that m^{6}A-binding protein YTHDF1 exerts a significant role in the progress of colorectal cancer. YTHDF2 was reported to be highly expressed in HCC tissues, whereas it was negatively correlated with the expression level of miR145. Luciferase assay showed that miR145 directly targeted 3'-UTR of YTHDF2 mRNA, and over-expression of miR145 down-regulated the levels of YTHDF217 at both mRNA and protein levels in HepG2 cells [53].

Conclusion

Recent studies have shown that proteins, modified by m^{6}A, play essential roles in various types of cancers, including leukemia, glioblastoma, breast cancer, lung cancer, hepatocellular carcinoma, renal cell carcinoma, and others (**Table 1**). Intriguingly, some proteins may exert similar influence on different types of cancers, while some others may function differently in similar types of cancers. FTO, for instance, has been shown to play an oncogenic role both in

leukemia and GBM; on the contrary, ALKBH5 functions as an oncogene in GBM and breast cancer and plays a tumor-suppressor role in leukemia. Similarly, METTL3 has a tumor-promoting role in lung cancer and tumor-suppressor role in GBM. Both FTO and WTAP exert oncogenic role in various subtypes of AML. Additionally, both METTL3 and METTL14 are highly expressed in AML and appear to behave as oncogenes. Together, these findings indicate that FTO and m^{6}A methyltransferases may not perform opposing functions in same type of cancers.

Similarly, DNMT3A and TET2 (DNA methyltransferases and demethylases), have a tumor-suppressor role in leukemia [54, 55] and inhibit the differentiation of HSC spectrum [56]. Methyltransferases and demethylases of m^{6}A modification may function similarly in different types of cancer by regulating distinct target genes. Hence, it is of great significance to study the biological function of genes, mediated by m^{6}A, in different types of cancer and identify their key target genes to understand the potential molecular mechanisms.

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Disclosure of conflict of interest

None.

Abbreviations

m^{6}A, N6-methyladenine; m^{7}G, N7-methylguanine; m^{5}C, 5-methylcytosine; m^{1}A, N1-methyladenine; Nm, 2'-O-Methylation modification; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; WTAP, Wilms' tumor 1-associated protein; FTO, fat mass and obesity-associated protein; ALKBH5, AlkB homolog 5; MeRIP-seq, Methylated RNA Immunoprecipitation sequencing; YTH, YT521-B homolog; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein; 3'-UTR, 3'-untranslated region; ncRNA, non-coding RNA; mRNA, messenger RNA; lncRNA, long non-coding RNA; rRNA, ribosomal RNA; tRNA, transfer RNA; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; CDS, coding sequence; SAM, S-adenosyl methionine; NSCLC, non-small cell lung cancer; HUR, Human antigen R; AML, acute myeloid leukemia; miCLIP, m^{6}A individual-nucleotide-resolution UV cross-linking and immunoprecipitation; HSPCs, hematopoietic stem/progenitor cells; LSCS/LICs, leukemia stem/initiation cells; HCC, hepatocellular carcinoma; CDK2, cycle-dependent kinase 2; ASB2, SOCS box-containing 2; RARA, retinoic acid receptor-α; ATRA, all-trans retinoic acid; GSC, glioblastoma; FOXM1, forkhead box M1; BCSCs, breast cancer stem cells; RFS, recurrence-free survival; YTHDC1, YTH domain containing 1; miRNA, microRNA; RBP, RNA-binding protein.

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