

REVIEW

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# The role of m<sup>6</sup>A RNA methylation in human cancer



Xiao-Yu Chen, Jing Zhang\* and Jin-Shui Zhu\*

## Abstract

N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) is identified as the most common, abundant and conserved internal transcriptional modification, especially within eukaryotic messenger RNAs (mRNAs). M<sup>6</sup>A modification is installed by the m<sup>6</sup>A methyltransferases (METTL3/14, WTAP, RBM15/15B and KIAA1429, termed as “writers”), reverted by the demethylases (FTO and ALKBH5, termed as “erasers”) and recognized by m<sup>6</sup>A binding proteins (YTHDF1/2/3, IGF2BP1 and HNRNPA2B1, termed as “readers”). Accumulating evidence shows that, m<sup>6</sup>A RNA methylation has an outsize effect on RNA production/metabolism and participates in the pathogenesis of multiple diseases including cancers. Until now, the molecular mechanisms underlying m<sup>6</sup>A RNA methylation in various tumors have not been comprehensively clarified. In this review, we mainly summarize the recent advances in biological function of m<sup>6</sup>A modifications in human cancer and discuss the potential therapeutic strategies.

**Keywords:** N<sup>6</sup>-methyladenosine, Cancer, RNA methylation, Prognosis, Growth, Metastasis

## Introduction

According to MODOMICS, 163 different chemical modifications in RNA have been identified in all living organisms by the end of 2017 [1]. Among these modifications, N<sup>6</sup>-methyladenosine (m<sup>6</sup>A), methylated at the N<sup>6</sup> position of adenosine, has been considered as the most pervasive, abundant and conserved internal transcriptional modification within eukaryotic messenger RNAs (mRNAs) [2], microRNAs (miRNAs) [3] and long non-coding RNAs (lncRNAs) [4]. RNA m<sup>6</sup>A is enriched near stop codon and 3' untranslated terminal region (UTR) [5, 6] and translated near 5' UTR in a cap-independent manner [7], thereby affecting RNA transcription, processing, translation and metabolism.

The deposition of m<sup>6</sup>A is encoded by a methyltransferase complex involving three homologous factors jargonized as ‘writers’, ‘erasers’ and ‘readers’ (Fig. 1). Methyltransferase-like 3 (METTL3) [8], METTL14 [9], Wilms tumor 1-associated protein (WTAP) [10], RBM15/15B [11] and KIAA1429 [12] are categorized as the components of ‘writers’ that catalyze the formation of m<sup>6</sup>A; ‘erasers’, fat mass and obesity-associated protein (FTO) [13] and alkB homologue 5 (ALKBH5) [14], selectively remove the

methyl code from target mRNAs; ‘Readers’ are capable of decoding m<sup>6</sup>A methylation and generating a functional signal, including YT521-B homology (YTH) domain-containing protein [15], eukaryotic initiation factor (eIF) 3 [11], IGF2 mRNA binding proteins (IGF2BP) families [16] and heterogeneous nuclear ribonucleoprotein (HNRNP) protein families [17]. YTH domain can recognize m<sup>6</sup>A through a conserved aromatic cage [18] and another two proteins FMR1, LRPPRC “read” this modification [19, 20]. Contrary to the conventional ‘writer’-‘eraser’-‘reader’ paradigm, few studies reveal METTL3/16 as a m<sup>6</sup>A ‘writer’ or ‘reader’ [21].

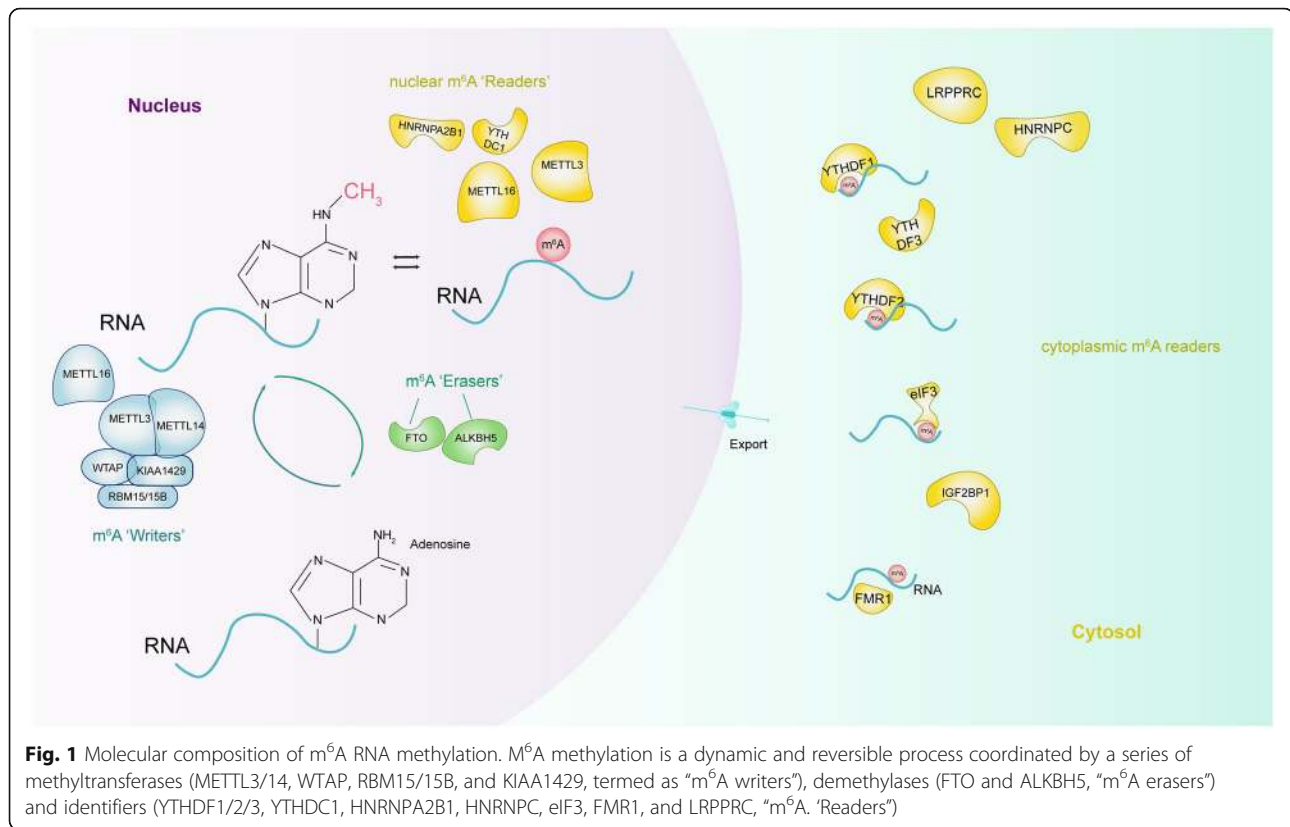
M<sup>6</sup>A RNA modification is a dynamic and reversible process which was corroborated by the discovery of ‘eraser’ in 2011 [13]. It is associated with multiple diseases such as obesity, infertility and cancer [22]. In this review, we summarize the function and therapeutic advances of m<sup>6</sup>A modifications in human cancer and provide their promising applications in the treatment of these malignant tumors (Table 1).

## Biological function of m<sup>6</sup>A modification in mammals

Recent years have witnessed a substantial progress of m<sup>6</sup>A post-transcriptional modification in regulating RNA transcription [23, 24], processing event [25–27],

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splicing [28–33], RNA stabilities [34–40] and translation [42–49] (Fig. 2).

#### M<sup>6</sup>A modification in RNA transcript

METTL3 and FTO are implicated in regulating transcription of CCAAT-enhancer binding protein (CEBP) family. METTL3 is localized to the starting sites of CEBPZ, which is required for recruitment of METTL3 to chromatin [23]. CEBPA is identified as an exclusive transcription factor displaying a positive correlation with FTO and regulating its transcription in acute myeloid leukemia (AML) [24].

#### M<sup>6</sup>A modification in RNA processing

M<sup>6</sup>A modifications promote the initiation of miRNA biogenesis [3] and regulate nuclear mRNA processing events [25]. METTL3 recognizes the pri-miRNAs by microprocessor protein DGCR8 and causes the elevation of mature miRNAs and concomitant reduction of unprocessed pri-miRNAs in breast cancer [3]. METTL14 interacts with DGCR8 to modulate pri-miR-126 and suppresses the metastatic potential of hepatocellular carcinoma (HCC) [26]. FTO can regulate poly(A) site and 3' UTR length by interacting with METTL3 [25]. YTHDC1 knockout in oocytes exhibits massive defects and contributes to extensive alternative polyadenylation and 3' UTR length alterations [27].

#### M<sup>6</sup>A modification in RNA splicing

M<sup>6</sup>A RNA modifications that overlap in space with the splicing enhancer regions affect alternative RNA splicing by acting as key pre-mRNA splicing regulators [28]. Inhibition of m<sup>6</sup>A methyltransferase impacts gene expression and alternative splicing patterns [29]. FTO regulates nuclear mRNA alternative splicing by binding with SRSF2 [25]. FTO and ALKBH5 regulate m<sup>6</sup>A around splice sites to control the splicing of Runt-related transcription factor 1 (RUNX1T1) in exon [28], and removal of m<sup>6</sup>A by FTO reduces the recruitment of SRSF2 and prompts the skipping of exon 6, leading to a short isoform of RUNX1T1 [30]. Depletion of METTL3 is associated with RNA splicing in pancreatic cancer [31]. WTAP is enriched in some proteins involved in pre-mRNA splicing [32]. But, some studies show that, M<sup>6</sup>A is not enriched at the ends of alternatively spliced exons and METTL3 unaffected pre-mRNA splicing in embryonic stem cells [33].

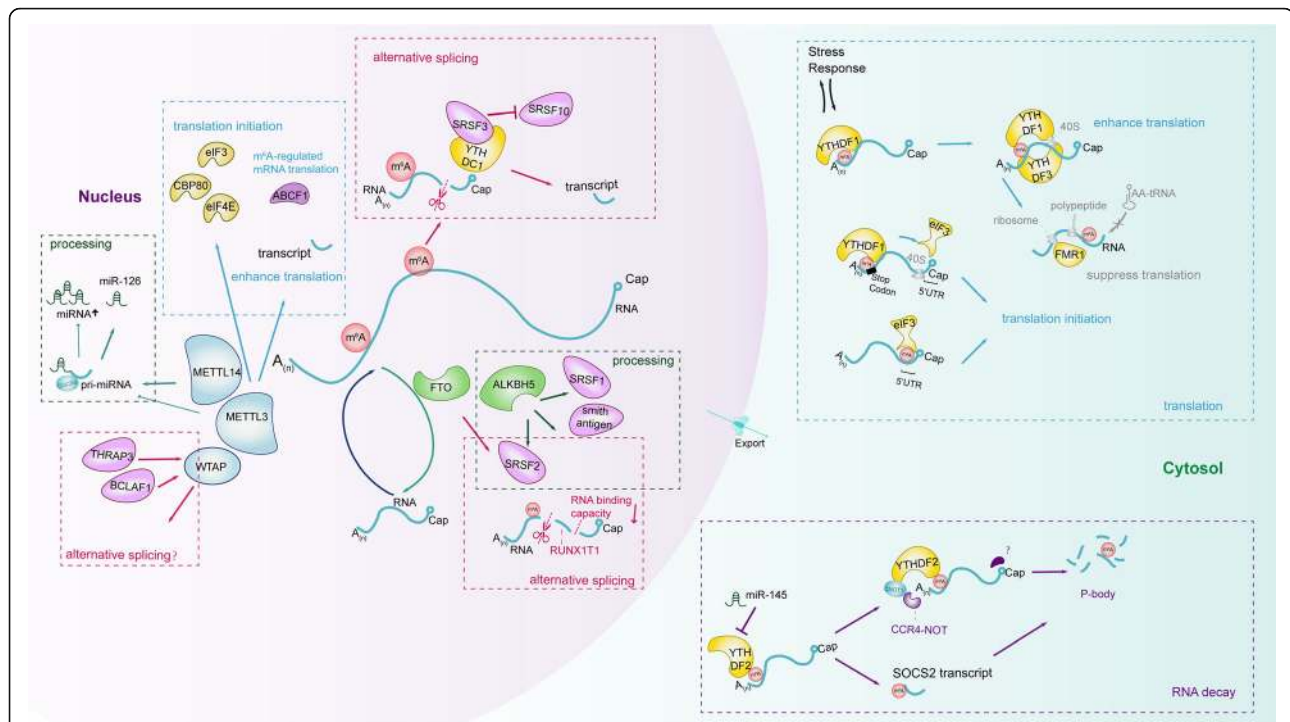
#### M<sup>6</sup>A modification in RNA degradation

M<sup>6</sup>A is a determinant of cytoplasmic mRNA stability [34], and reduces mRNA stability [35]. A RNA decay monitoring system is adopted to investigate the effects of m<sup>6</sup>A modifications on RNA degradation [36]. Knock-down of METTL3 abolishes SOCS2 m<sup>6</sup>A modification and augments SOCS2 expression [37]. M<sup>6</sup>A-mediated

**Table 1** Multiple functions exerted by m<sup>6</sup>A RNA methylation in various diseases

Disease	Related targets	M <sup>6</sup> A component	Function	Role in diseases	Source of experimental evidence	Regulation	Year	Refs
AML	c-MYC, BCL2, PTEN	METTL3	Writers	oncogene	HSPCs, AML MOLM-13 cells	Up-regulation	2017	[70]
AML	CEBPZ	METTL3	Writers	oncogene	AML cells, immunodeficient mice	Up-regulation	2017	[23]
AML	MYB, MYC	METTL14	Writers	oncogene	AML cell lines	Up-regulation	2017	[68]
AML	mTOR	WTAP	Writers	oncogene	511 newly diagnosed AML patient samples, Ba/F3 cell line, AML cell lines	Down-regulation	2014	[69]
AML	ASB2, RARA	FTO	Erasers	oncogene	MONOMAC-6 and NB4 cells	Down-regulation	2017	[67]
AML	MYC, CEBPA	FTO	Erasers	oncogene	27 human leukemia cell lines	Up-regulation	2018	[24]
AML	Tal1...	YTHDF2	Readers	anti- oncogene	HSPCs, mouse...	Down-regulation	2018	[72]
Bladder cancer	AFF4, MYC	METTL3	Writers	oncogene	Bladder cancer cell lines, mouse bladder cancer samples	Up-regulation	2019	[44]
Breast cancer	HBXIP	METTL3	Writers	oncogene	24 clinical tumor samples, MCF-7, MDA-MB-468 cells	Up-regulation	2018	[78]
Breast cancer	NANOG	ALKBH5	Erasers	oncogene	BCSCs	Up-regulation	2016	[79]
CRC	WT1, TBL1	WTAP	Writers	oncogene	115 patient samples with CRC, colon cancer cell lines	Down-regulation	2016	[81]
Endometrial cancer	AKT...	METTL3/14	Writers	anti- oncogene	Cancer samples, endometrial cancer cell lines, mice	Down-regulation	2018	[66]
GBM	ADAM19	METTL3/14	Writers	anti- oncogene	GSC, GSC-grafted mice	Down-regulation	2017	[74]
GBM	FOXM1	ALKBH5	Erasers	oncogene	GSCs	Up-regulation	2017	[73]
HCC	SOC2	METTL3	Writers	oncogene	MHCC97L, Huh-7 and HepG2 cell lines, BABL/cAnN-nude mice	Down-regulation	2017	[37]
HCC	miR-126	METTL14	Writers	anti- oncogene	HepG2 cell	Up-regulation	2017	[26]
HCC	miR-145	YTHDF2	Readers	oncogene	clinical tissue, HepG2 cell line	miR-145 suppresses YTHDF2	2017	[77]
HCC, AML...	SRF...	IGF2BP1	Readers	oncogene	HepG2, K562, hESCs cell lines...	Up-regulation	2019	[16]
impaired fertility	Uhrf1...	ALKBH5	Erasers	spermatogenesis	HeLa cells, mouse testicular cells	Up-regulation	2013	[14]
Lung cancer	EGFR, TAZ	METTL3	Writers	oncogene	Human lung cancer cell lines, HeLa, HEK293T cells	Up-regulation	2016	[46]
NPC	ZNF750, FGF14	METTL3	Writers	oncogene	NPC biopsy samples and cell lines	Down-regulation	2018	[45]
Obesity	SRSF2	FTO	Erasers	adipogenesis	3 T3-L1 cell	Decreased RNA binding ability	2014	[28]
Pancreatic cancer	RBM17...	METTL3	Writers	oncogene	Pancreatic cancer cell lines	Up-regulation	2018	[31]

HSPCs hematopoietic stem/progenitor cells, AML acute myeloid leukemia, GBM Glioblastoma, GSC glioblastoma, HCC hepatocellular cancer, CRC colorectal cancer, BCSCs Breast cancer stem cells, NPC Nasopharyngeal carcinoma



**Fig. 2** Regulatory Functions of m<sup>6</sup>A modification in RNA splicing, processing, translation and degradation. M<sup>6</sup>A RNA modification is involved in regulating the life cycle of RNA including RNA splicing (regulated by WTAP, FTO, ALKBH5 and YTHDC1), RNA processing (regulated by METTL3/14 and ALKBH5), RNA translation (regulated by METTL3, YTHDF1/3, eIF3 and FMR1) and RNA degradation (regulated by YTHDF2)

SOCS2 degradation also relies on m<sup>6</sup>A ‘reader’ YTHDFs [37], which accelerate the decay of m<sup>6</sup>A-modified transcripts [38] or target mRNA [39]. Knockout of m<sup>6</sup>A methyltransferase attenuates YTHDF2 specific binding with target mRNAs and increases their stability [40]. M<sup>6</sup>A RNA methylation also controls T cell homeostasis by targeting the IL-7/STAT5/SOCS pathways [41] and decreases the stability of MYC/CEBPA transcripts [24].

#### M<sup>6</sup>A modification in RNA translation

M<sup>6</sup>A modifications occur in mRNA and noncoding RNA (ncRNAs) to regulate gene expression in its 5′ or 3′ UTR [7, 42]. METTL3 enhances mRNA translation [8], while depletion of METTL3 selectively inhibits mRNAs translation in 5′UTR [43] and reduces AFF4 and MYC translation in bladder cancer [44] but increase that of zinc finger protein 750 and fibroblast growth factor 14 in nasopharyngeal carcinoma [45].

M<sup>6</sup>A modifications facilitate the initiated translation through interacting with the initiation factors eIF3, CBP80 and eIF4E in an RNA-independent manner [46]. Heat-shock-induced translation of heat-shock protein 70 (HSP70) alters the transcriptome-wide distribution of m<sup>6</sup>A [7] and affects DNA repair [47]. ABCF1-sensitive transcripts largely overlaps with METTL3-modified mRNAs and are critical for m<sup>6</sup>A-regulated mRNA translation [43]. In addition, FMR1 binds to hundreds of

mRNAs to negatively regulate their translation [20]. YTHDF1 facilitates the translation of m<sup>6</sup>A-modified mRNAs in protein-synthesis and YTHDF3 acts in the initial stage of m<sup>6</sup>A-driven translation from circular RNAs (circRNAs) [38, 48, 49].

#### M<sup>6</sup>A RNA modification in metabolic and developmental diseases

The methyltransferases and demethylases of m<sup>6</sup>A are associated with a variety of diseases, such as obesity [13, 50], type 2 diabetes mellitus (T<sub>2</sub>DM) [51], growth retardation, developmental delay, facial dysmorphism [52]. Besides, m<sup>6</sup>A modification affects infertility [14], developmental arrest [22], neuronal disorder [53] and infectious diseases [54, 55].

#### M<sup>6</sup>A modification in metabolic and infectious diseases

M<sup>6</sup>A modification is involved in metabolic abnormalities in patients with T<sub>2</sub>DM and obesity [56]. FTO regulates the energy homeostasis and dopaminergic pathway through FTO-dependent m<sup>6</sup>A demethylation [50, 51], and it is ubiquitous in adipose and muscle tissues, influencing RUNX1T1 splicing in adipogenesis [28, 30]. METTL3/14 reduce the abundance of Hepatitis C virus replication, but FTO promotes its production through YTHDF proteins [54]. M<sup>6</sup>A is also identified as a conserved modulatory symbol

across Flaviviridae genomes, including dengue, Zika virus and West Nile virus [55].

#### ***M<sup>6</sup>A modification in infertility***

Deficiency of demethylase ALKBH5 leads to the aberrant spermatogenesis and apoptosis with impaired fertility in testes and striking changes in DNA methyltransferase 1 (Dnmt1) and ubiquitin-like with PHD and RING finger domains 1 (Uhrf1) [14]. YTHDF2 is required for maternal transcriptome during oocyte maturation [57]. YTHDC1/2 determine the germline development in mouse [58], and YTHDC1 is essential for spermatogonia in males and oocyte maturation in females [27].

#### ***M<sup>6</sup>A modification in nervous system development***

M<sup>6</sup>A modification regulates the pace of cerebral cortex development [59] and m<sup>6</sup>A-regulated histone modifications enhances self-renewal of neural stem cells by METTL3/14 [60]. M<sup>6</sup>A has dual effects on delaying tempo of corticogenesis by two distinct pathways: increased cell-cycle length and decreased mRNA decay [59]. M<sup>6</sup>A depletion decreases the decay of radial glia cells associated with stem cell maintenance, neurogenesis and differentiation [61].

#### ***M<sup>6</sup>A modification in inflammation and metabolism-related cancer***

Carcinogenesis is characterized by stepwise accumulation of genetic/epigenetic alterations of different proto-oncogenes and tumor-suppressor genes following other diseases including chronic inflammation and metabolic diseases. METTL3/14 and FTO influence Hepatitis C virus replication and production, and endogenous mediators of inflammatory responses (proinflammatory cytokines, reactive oxygen, et al) can promote genetic/epigenetic alterations [62]. FTO affects RUNX1T1 splicing in adipogenesis [28, 30], and RUNX1T1 is essential for pancreas development [63]. Transcription factor forkhead box protein O1 (FOXO1) as another direct substrate of FTO, regulates gluconeogenesis in liver [64] and promotes the growth of pancreatic ductal adenocarcinoma [65].

#### ***M<sup>6</sup>A RNA modification in human cancer***

Emerging evidence suggests that, m<sup>6</sup>A modification is associated with the tumor proliferation, differentiation, tumorigenesis [46], proliferation [66], invasion [46] and metastasis [26] and functions as oncogenes or anti-oncogenes in malignant tumors (Table 1 and Fig. 3).

#### ***Acute myeloid leukemia (AML)***

FTO is highly expressed in AML with t(11q23)/MLL rearrangements, t(15;17)/PML-RARA, FLT3-ITD and/or

NPM1 mutations and promotes leukemic cell transformation and tumorigenesis [67]. METTL3/14 are expressed in hematopoietic stem/progenitor cells (HSPCs) and AML cells with t(11q23), t(15;17), or t(8;21), control the terminal myeloid differentiation of HSPCs and promote the survival and proliferation of AML [68]. WTAP acts in cell proliferation and arrests the differentiation of leukemia [69].

M<sup>6</sup>A promotes the translation of *c-MYC*, *BCL2* and *PTEN* in AML [70]. METTL14 acts an oncogenic role by regulating its targets MYB/MYC through m<sup>6</sup>A modification [68]. YTHDF2, responsible for the decay of m<sup>6</sup>A-modified mRNA transcripts [40], is also associated with MYC in leukemia [71]. Besides, YTHDF2 stabilizes Tal1 mRNAs and increases its expansion in AML [72].

Collectively, these studies corroborate the functional importance of m<sup>6</sup>A modifications in leukemia, such as METTL3 [23, 70], METTL14 [68], FTO [24, 67] and YTHDF2 [24, 40] and they provide profound insights into development and maintenance of AML and self-renewal of leukemia stem/initiation cells through the downstream MYC and Tal1 pathways.

#### ***Glioblastoma (GBM)***

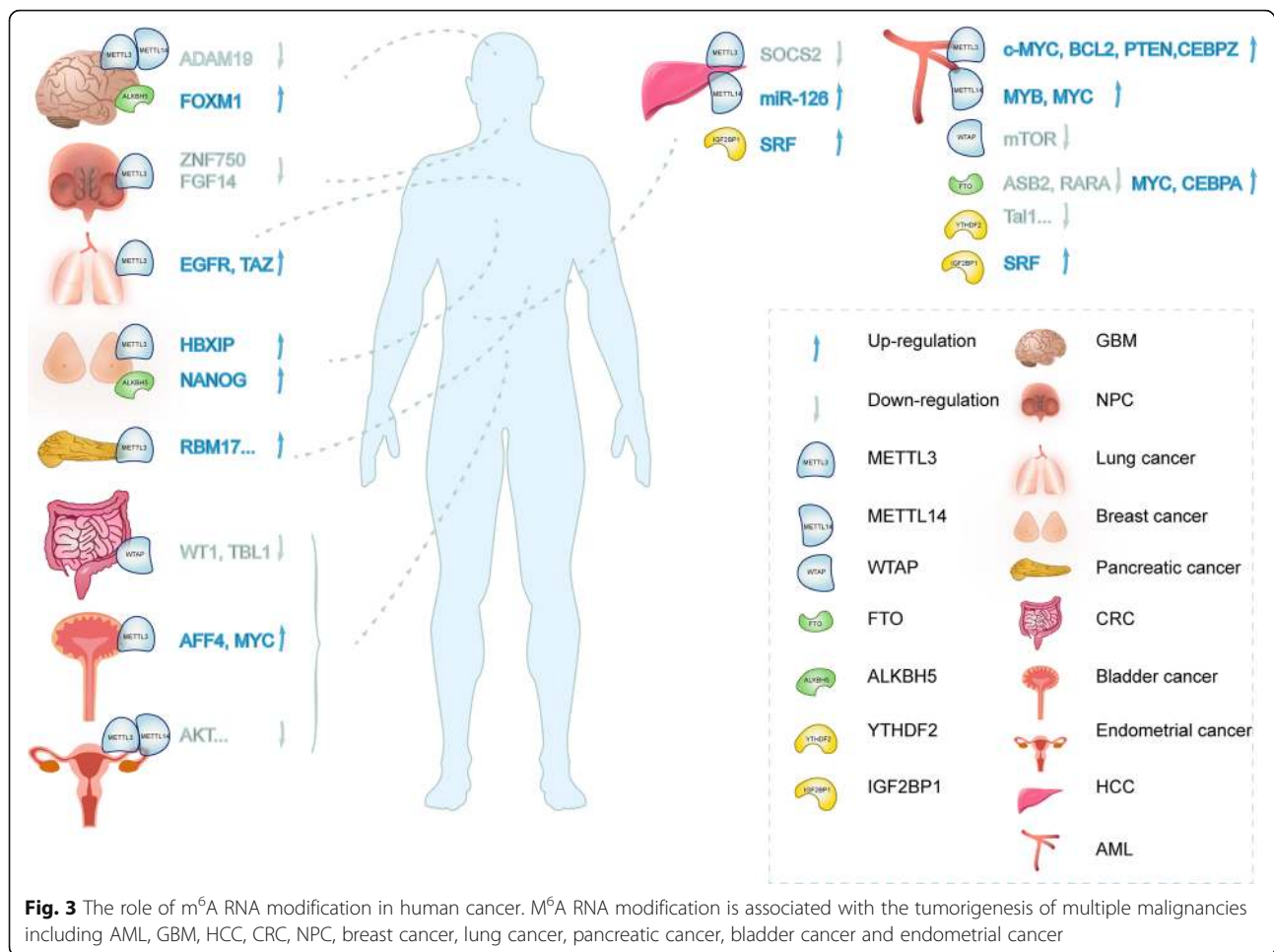
METTL3/14 inhibit GSC growth, self-renewal and tumorigenesis, but FTO and ALKBH5 indicate poor survival in GBM by regulating ADAM19 and transcription factor FOXM1 [73, 74]. LncRNA antisense to FOXM1 (FOXM1-AS) promotes the interaction of ALKBH5 with FOXM1 nascent transcripts in the tumorigenesis of GSCs [73].

#### ***Lung cancer***

M<sup>6</sup>A demethylase FTO is identified as a prognostic factor in lung squamous cell carcinoma (LUSC) and facilitates cell proliferation and invasion, but inhibits cell apoptosis by regulating MZF1 expression [75]. METTL3 acts as a oncogene in lung cancer by increasing EGFR and TAZ expression and promoting cell growth, survival and invasion [46]. METTL3-eIF3 caused mRNA circularization promotes the translation and oncogenesis of lung adenocarcinoma [46]. Besides, SUMOylation of METTL3 is of importance for the promotion of tumor growth at lysine residues K<sup>177</sup>, K<sup>211</sup>, K<sup>212</sup> and K<sup>215</sup> in non-small cell lung carcinoma (NSCLC) [76]. These studies provide insights into the critical roles of METTL3 and FTO in lung carcinoma.

#### ***Hepatocellular carcinoma (HCC)***

METTL3 is related to a poor prognosis in HCC patients and promotes HCC cell proliferation, migration and colony formation by YTHDF2-dependent posttranscriptional silencing of SOCS2 [37]. But, METTL14 is an anti-metastatic factor and serves as a favorable factor in



HCC by regulating m<sup>6</sup>A-dependent miRNA processing [26]. MiR-145 down-regulates YTHDF2 through targeting its mRNA 3' UTR [77]. In conclusion, METTL3 up-regulation or METTL14 downregulation predicts poor prognosis in patients with HCC and contributes to HCC progression and metastasis [26, 37]. METTL3 suppresses SOCS2 expression in HCC via the miR-145/m<sup>6</sup>A/YTHDF2 dependent axis [37, 77]. Thus, these studies suggest a new dimension of epigenetic alteration in liver carcinogenesis.

#### Breast cancer and colorectal cancer (CRC)

METTL3 is associated with the expression of mammalian hepatitis B X-interacting protein (HBXIP), displaying an aggressiveness in breast cancer. HBXIP-induced METTL3 promotes the proliferation of breast cancer via inhibiting tumor suppressor let-7g [78]. Besides, ALKBH5 decreases the levels of m<sup>6</sup>A in NANOG mRNA and enhances its stability, leading to an increase of NANOG mRNA and protein levels in breast cancer stem cells (BCSCs) [79]. Another m<sup>6</sup>A eraser 'FTO' polymorphism has no association with the risk of CRC [80], but the m<sup>6</sup>A 'writer'

WTAP is associated with carbonic anhydrase IV (CA4), which inhibits the proliferation and induces apoptosis and cycle arrest by repressing the Wnt signaling through targeting the WTAP-WT1-TBL1 axis [81].

#### Brief summary of m<sup>6</sup>A modification-related carcinogenesis

m<sup>6</sup>A RNA modifications regulate RNA production/metabolism and take part in the carcinogenesis. On the one hand, m<sup>6</sup>A-modified genes usually act a oncogenic role in cancer, leading to alterations of mRNA translation and acceleration of tumor progression, and decreasing m<sup>6</sup>A modification results in tumor development. On the other hand, given that SUMOylation of METTL3 represses its m<sup>6</sup>A methyltransferase capacity and results in tumor growth of NSCLC, modification of m<sup>6</sup>A methylase can determine the tumor development.

#### M<sup>6</sup>A modification in cancer treatment

m<sup>6</sup>A modification indicates new directions for the treatment of various cancers. Regulators or inhibitors of m<sup>6</sup>A modifications may provide the potential therapeutic strategies for cancers, such as MA2 in GBM [74],

R-2HG/SPI1/FB23–2 in AML [24, 68, 82] and CA4 in CRC [81]. Meclofenamic acid (MA) as one of the selective FTO inhibitors is a non-steroidal anti-inflammatory drug by competing with FTO binding sites [83]. MA2, the ethyl ester derivative of MA, increases m<sup>6</sup>A modification, leading to the suppression of tumor progression [74, 83]. The expression of ASB2 and RARA is increased in hematopoiesis and they act as key regulators of ATRA-induced differentiation of leukemia cells [84]. FTO enhances the leukemogenesis of AML by inhibition of the ASB2 and RARA expression [67]. FB23–2, as another inhibitor of m<sup>6</sup>A demethylase FTO suppresses AML cell proliferation and promotes the cell differentiation and apoptosis [82].

ALKBH5 and FTO are  $\alpha$ -ketoglutarate ( $\alpha$ -KG)-dependent dioxygenases [85], which are competitively inhibited by D2-hydroxyglutarate (D2-HG) and elevated in isocitrate de-hydrogenases (IDH)-mutant cancers for transferring isocitrate to  $\alpha$ -KG [86]. R-2-hydroxyglutarate (R-2HG), an metabolite by mutating IDH1/2 enzyme, exhibits anti-leukemia effects through increasing m<sup>6</sup>A levels in R-2HG-sensitive AML [24].

S-adenosylmethionine (SAM) serves as a cofactor substrate in METTL3/14 complex and its product S-adenosylhomocysteine (SAH) inhibits the methyltransferases by competing with adenosylmethionine [87]. 3-deazaadenosine (DAA) inhibits SAH hydrolase and interrupts insertion of m<sup>6</sup>A into mRNA substrates [88] and its analogs suppress the replication of various viruses editing m<sup>6</sup>A- mRNA in cancers [89, 90].

METTL14 acts an oncogenic role by regulating MYB/MYC axis through m<sup>6</sup>A modification [68]. SPI1, a hematopoietic transcription factor, directly inhibits METTL14 expression in malignant hematopoietic cells [68] and may be a potential therapeutic target for AML. CA4 inhibits the tumorigenicity of CRC by suppressing the WTAP-WT1-TBL1 axis [81].

#### Future prospect

m<sup>6</sup>A RNA modifications act by regulating RNA transcript, splicing, processing, translation and decay and participate in the tumorigenesis and metastasis of multiple malignancies. However, the underlying mechanisms of m<sup>6</sup>A modifications in cancer should be further addressed. Besides FMR1 and LRPPRC, the function of ALKBH family in m<sup>6</sup>A RNA methylation is undetermined. METTL14 has different expression levels in various tumor tissues. Given a dual role of METTL14 either as a tumor suppressor [26] or an oncogene in cancer [68], its role in other cancers need be further elucidated. Though some inhibitors of m<sup>6</sup>A methylation have shown promising effects on cancer development [68, 81], novel therapeutic strategies for m<sup>6</sup>A RNA methylation should be further explored in the treatment of cancer.

#### Abbreviations

ALKBH5: Alkb homologue 5; AML: Acute myeloid leukemia; BCLAF1: BCL2-associated transcription factor 1; BCSCs: Breast cancer stem cells; CA4: Carbonic anhydrase IV; CEBP: CCAAT-enhancer binding protein; circRNAs: Circular RNAs; CRC: Colorectal cancer; D2-HG: D2-hydroxyglutarate; DAA: 3-deazaadenosine; Dnmt1: DNA methyltransferase 1; eIF: eukaryotic initiation factor; FGF14: Fibroblast growth factor 14; FOXM1-AS: Antisense to FOXM1; FOXO1: Forkhead box protein O1; FTO: Fat mass and obesity-associated protein; GSCs: Glioblastoma stem-like cells; HBXIP: Hepatitis B X-interacting protein; HCC: Hepatocellular carcinoma; HNRNP: Heterogeneous nuclear ribonucleoprotein; HSP70: Heat-shock protein 70; HSPCs: Hematopoietic stem/progenitor cells; IDH: Isocitrate de-hydrogenases; IGF2BP: IGF2 mRNA binding proteins; lncRNAs: Long non-coding RNAs; LUSC: Lung squamous cell carcinoma; m<sup>6</sup>A: N<sup>6</sup>-methyladenosine; MA: Meclofenamic acid; METTL3: Methyltransferase-like 3; miRNAs: Micro RNAs; mRNAs: Messenger RNAs; ncRNAs: Noncoding RNAs; NSCLC: Non-small cell lung carcinoma; R-2HG: R-2-hydroxyglutarate; RUNX1T1: Runt-related transcription factor 1; SAH: S-adenosylhomocysteine; SAM: S-adenosylmethionine; SOCS2: Suppressor of cytokine signaling 2; SRSF: serine/arginine-rich splicing factor; T<sub>2</sub>DM: Type 2 diabetes mellitus; THRAP3: Thyroid hormone receptor-associated protein 3; Uhrf1: Ubiquitin-like with PHD and RING finger domains 1; UTR: Untranslated terminal region; WTAP: Wilms tumour 1-associated protein; YTHDF: YTHDF1-3 homology domain-containing protein family; ZNF750: Zinc finger protein 750;  $\alpha$ -KG:  $\alpha$ -ketoglutarate

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#### Authors' contributions

JZ and JSZ designed this study and XYZ drafted the manuscript. JZ revised this manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

All data generated or analyzed during this study are included in this published article and its additional files.

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

All of the authors are aware of and agree to the content of the paper and their being listed as a co-author of the paper.

#### Competing interests

The authors declare that they have no competing interests.

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