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Mini review

N^1-methyladenosine modification in cancer biology: Current status and future perspectives

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ABSTRACT

Post-transcriptional modifications in RNAs regulate their biological behaviors and functions. N^1-methyladenosine (m^1A), which is dynamically regulated by writers, erasers and readers, has been found as a reversible modification in tRNA, mRNA, rRNA and long non-coding RNA (lncRNA). m^1A modification has impacts on the RNA processing, structure and functions of targets. Increasing studies reveal the critical roles of m^1A modification and its regulators in tumorigenesis. Due to the positive relevance between m^1A and cancer development, targeting m^1A modification and m^1A-related regulators has been of attention. In this review, we summarized the current understanding of m^1A in RNAs, covering the modulation of m^1A modification in cancer biology, as well as the possibility of targeting m^1A modification as a potential target for cancer diagnosis and therapy.

Contents

Abbreviations: m^1I, 1-methylinosine; UTR, 5′ untranslated region; hm^5C, 5-hydroxymethylcytosine; m^5C, 5-methylcytidine; AAA, Abdominal aortic aneurysm; ALKBH1, Alkb homologue 1; ALKBH3, Alkb homologue 3; ALKBH7, Alkb homologue 7; AML, Acute myeloid leukemia; BC, Breast cancer; BLCA, Bladder urothelial carcinoma; CC, Colon cancer; CRC, Colorectal cancer; cyt-tRNA, Cytoplasmic tRNA; FTO, Fat mass and obesity-associated protein; GBM, Glioblastoma multiforme; GI, Gastrointestinal cancer; HCC, Hepatocellular carcinoma; lncRNA, Long non-coding RNA; MA2, Meclofenamic acid 2; mt-tRNA, Mitochondrial tRNA; m^1A, N^1-methyladenosine; m^6Am, N^6,2′-*O*-dimethyladenosine; m^6A, N^6-methyladenosine; m^7G, N^7-methylguanosine; NSAID, Nonsteroidal anti-inflammatory drug; NSCLC, Non-small-cell lung cancer; NML, Nucleomethylin; OSCC, Oral squamous cell carcinoma; OC, Ovarian cancer; PAAD, Pancreatic cancer; PC, Prostate cancer; R-2HG, R-2-hydroxyglutarate; N_m, Ribose-methylation; SAM, S-adenosyl-L-methionine; tRFs, tRNA fragments; TRMT10C, tRNA methyltransferase 10C; TRMT6, tRNA methyltransferase 6; TRMT61A, tRNA methyltransferase 61A; TRMT61B, tRNA methyltransferase 61B; tDRs, tRNA-derived small RNAs; TME, Tumor microenvironment; YTH, YT521-B homology; YTHDC1, YTH domain containing 1; YTHDF1, YTH domain family protein 1; YTHDF2, YTH domain family protein 2; YTHDF3, YTH domain family protein 3.

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1. Introduction

Over 170 distinct chemical modifications have been identified in RNA, which post-transcriptionally and extensively regulate the behaviors and biological functions of RNAs. Methylation is the most frequent internal modification in RNA, including N^6-methyladenosine (m^6A), N^1-methyladenosine (m^1A), N^6,2′-*O*-dimethyladenosine (m^6Am), 5-methylcytidine (m^5C), 5-hydroxymethylcytosine (hm^5C), N^7-methylguanosine (m^7G), and ribose-methylation (N_m). Among them, m^1A is a critical internal RNA modification that controls gene expression.

1) Discovery of m^1A methylation.

m^1A, which occurs on the first nitrogen atom of adenosine in RNA, is a ubiquitous RNA modification (Fig. 1). m^1A was first reported in 1961 [1]. Later, m^1A was found to exist in tRNAs [2], rRNAs [3–4], mRNAs [5–6], and long non-coding RNAs (lncRNAs) [7]. Among them, tRNA is the most heavy-modified class of RNA. In tRNA, N^1-methylation can occur on both purines (adenine and guanine), with m^1A occurring at a greater number of positions than m^1G [8]. In mRNA, m^1A is less prevalent compared with m^6A. The occurrence of m^1A in mRNA is about 6-fold less than that of m^6A in mRNA [9]. Interestingly, it was reported that the nitrogen atom could transfer from m^1A to m^6A after the Dimroth rearrangement under an alkaline environment [10], suggesting the potential joint regulation of RNA via the dynamic interaction between m^1A and m^6A.

2) Characterizations of m^1A methylation in RNAs.

m^1A was found to be an ancient RNA modification across Bacteria, Archaea and Eukarya. It has been identified in various RNA transcripts including Table 1: **i) tRNA:** m^1A modification occurs at positions 9, 14, 22, 57, and 58 of cytoplasmic tRNAs (cyt-tRNAs), and positions 9 and 58 in mitochondrial tRNAs (mt-tRNAs) [8,11–12]. The m^1A at position 58 (m^1A58) is the first m^1A modification of the initial transcripts of tRNA in the nucleus [13], and it is the most conserved and common in bacteria, archaea, and eukaryotes [14], especially that of eukaryotic initiator $tRNA^{iMet}$ [15]; m^1A14 is only found in a limited number of cytoplasmic cyt-$tRNA^{Phe}$ of mammals [16]; m^1A22 occurs only in bacterial tRNAs [17]; m^1A57 exists as an intermediate to 1-methylinosine (m^1I) by hydrolytic deamination in archaea [18]; and m^1A9 has been found in cyto-tRNA from archaea and mammalian mt-tRNAs such as mt-$tRNA^{Lys}$ and mt-$tRNA^{Asp}$ [19–20]. **ii) rRNA:** m^1A modification occurs in the bacterial and mitochondrial 16S rRNA, yeast 25S rRNA, and 28S rRNA in humans and mice [3,21]. Among them, m^1A is conserved in position 947 of the mitochondrial 16S rRNA of vertebrates [22]; m^1A645 in 25S rRNA of budding yeast and m^1A1322 in 28S rRNA of mammals are conserved [3]. **iii) mRNA:** over 900 transcripts containing m^1A modification were identified

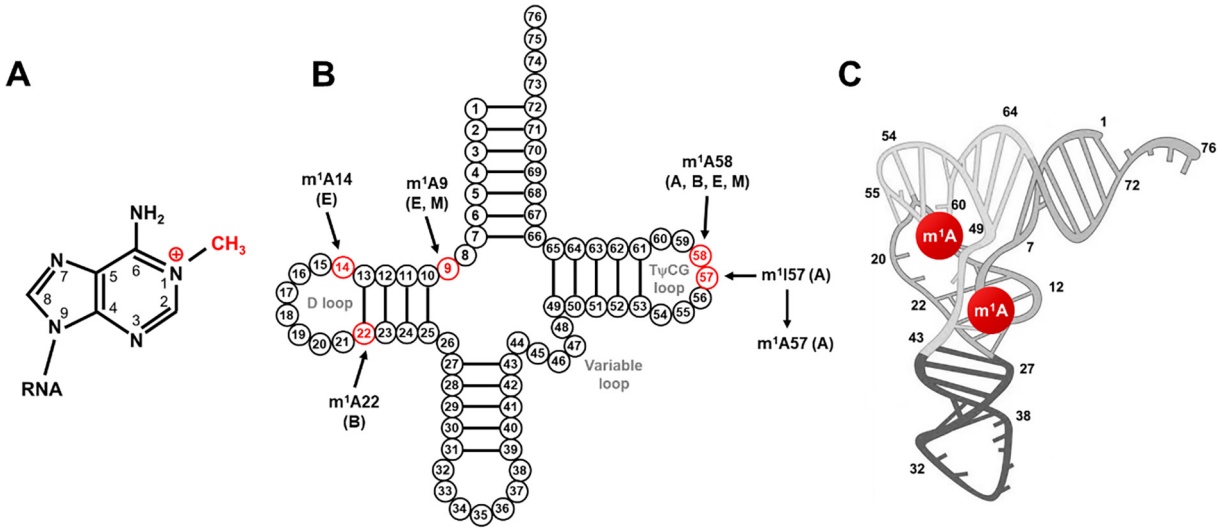

Fig. 1. M^1A methylation and its positions in tRNAs. (A) Chemical structure of the m^1A modification; (B) The m^1A methylation shown on a tRNA at reported modification sites (red). The domain in which the modification has been identified is indicated as A: archaea, E: eukaryotes, and B: bacteria. M indicates m^1A modifications found in mitochondria; (C) Location of m^1A modifications in human tRNA with tertiary structure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Overview of m^1A modifications in human RNAs.

RNA	Position	Functions
tRNA	9	Formation of cloverleaf structure; Stabilization of tRNA structure [35]
mt-tRNA	9	Formation of cloverleaf structure; Stabilization of tRNA structure [19,36]
$tRNA^{Phe}$	14	Unknown [16]
tRNA	58	Promotion of translation; Stabilization of $tRNA^{iMet}$ [15,29]
mt-tRNA	58	Unknown [12]
mt-16S rRNA	947	Stabilization of mitochondrial ribosome [22]
28S rRNA	1322	Formation of ribosome 60S subunit [37]
mRNA	All segments	Promotion of translation [9]
ATP5D mRNA	A71 at Exon 1	Suppression of translation elongation [38]
mt-mRNA	CDS	Prevent the effective translation of modified codons [6]
ND5 mt-mRNA	1374	Unknown [24]
MALAT1 lncRNA	8398	Unknown [24]

in eukaryotic cells [5]. The deposition of m^1A can occur along the mRNA, but most heavy-modified in the first splice site and the highly structured regions in the 5′ untranslated regions (UTRs) of mRNAs such as GC-rich regions [5]. Current reports suggest that each modified transcript contains on average one m^1A, and the ratio of m^1A/A is approximately 0.02 % in humans, which is relatively low compared to m^6A/A in mRNA [5,9,23]. In mitochondria, one single m^1A site in *ND5* mRNA is identified [24]. **vi) lncRNA:** recent study reveals that each m^1A methylated lncRNA had an average of 1.04 m^1A modification sites, where HGGAGRA and WGGANGA (H = A, U, or C, R = G or A) might be the m^1A motifs in lncRNA [7]. Nevertheless, m^1A in position 8398 of *MALAT1* has been the only validated m^1A modification in lncRNA [24].

3) Regulators of m^1A methylation in mammalian RNAs.

Similar to the dynamic modification of m^6A, m^1A is installed by methyl-transferases called "writer" (TRMT6, TRMT61A, TRMT61B, TRMT10C, and NML), removed by demethylases called "eraser" (ALKBH1, ALKBH3, ALKBH7, FTO), and recognized by m^1A-binding proteins called "reader" (YTHDF1, YTHDF2, YTHDF3, YTHDC1) [21,24–27]. Here, m^1A-related enzymes in human are focused on (Fig. 2). **i) Writer:** TRMT61A contains a methyl donor (S-adenosyl-L-methionine, SAM) binding pocket and functions as the catalytic subunit. TRMT61A forms a functional heterotetramer complex with TRMT6, which lacks SAM binding motif and is essential for tRNA-binding [28–29]. TRMT6/61A complex locates in the cytosol and seems to recognize targets in a structure-dependent manner. TRMT6/61A can methylate both cyto-tRNA m^1A58 (*T*-loop) and mRNAs with a *T*-loop-like structure, where with a GUUCRA tRNA-like motif[6]. TRMT61B methylases mitochondrial 16S rRNA [22], whilst recombinant TRMT10B can weakly methylate the A9 of $tRNA^{Asp(GTC)}$ *in vitro* [30]. TRMT61B likely recognizes its tRNA and rRNA targets by a similar mechanism, where a weak consensus sequence (YMRAW) is revealed surrounding targets [22]. TRMT10C installed mt-tRNA m^1A and/or m^1G at position 9 coupling with SDR5C1 [31]. NML, also known as RRP8, locates in nuclei and methylases the m^1A on 28S rRNA [21]. **ii) Eraser:** ALKBH1 demethylates most m^1A in cyto-tRNAs, except $tRNA^{Phe(GAA)}$ and $tRNA^{Sec(UCA)}$, and m^1A58 in tRNAs is a major substrate of ALKBH1 [15]. ALKBH3 performs demethylation of both m^1A and m^3C in tRNAs, as well as the m^1A demethylation in mRNA [5,27]. ALKBH7, which locates in mitochondria, can demethylate the m^1A and $m^{22}G$ in mitochondrial pre-$tRNA^{Leu1}$ and pre-$tRNA^{Ile}$ in the nascent polycistronic mitochondrial RNA [32]. FTO, the first discovered RNA m^6A demethylase, is found to bind multiple RNA species and perform demethylation including m^6A and m^6Am in mRNA and snRNA, and m^1A in tRNA [33]. **iii) Reader:** Four YT521-B homology (YTH) domain-containing proteins including YTHDF1, YTHDF2, YTHDF3, and YTHDC1 are recently identified as readers for m^1A modification, in spite of their roles of m^6A readers [24,26]. Their binding affinity with m^1A sites is weaker than that of m^6A. YTH domain is presented in 174 different proteins and is evolutionarily conserved across the eukaryotic species [34], suggesting that the YTH domain is one of the sufficient structures for the recognition of methyl-group in RNAs. Research on their functions acting as m^1A readers remained limited.

2. Functions of m^1A in RNAs

The methyl group in m^1A carries a positive electrostatic charge under physiological conditions [39], which can disrupt the Watson-Crick base pairing with uridine. The electro-chemical interaction of m^1A-modified RNAs may have impacts on the processing, structural formation, and biological functions of RNAs, as well as their interactions with potential partner proteins.

1) Alteration of pre-RNA processing: m^1A58 can be found in both mt-tRNA and mt-dsRNA. Within the mitochondrial Leu1 pre-tRNA region, m^1A58 is partially methylated and can be demethylated by ALKBH7, whilst the m^1A9 level is not affected. Knockdown of ALKBH7 reduces the total mt-tRNA level through degradation of pre-tRNA and nascent mt-mRNA (mt-dsRNA) [32],

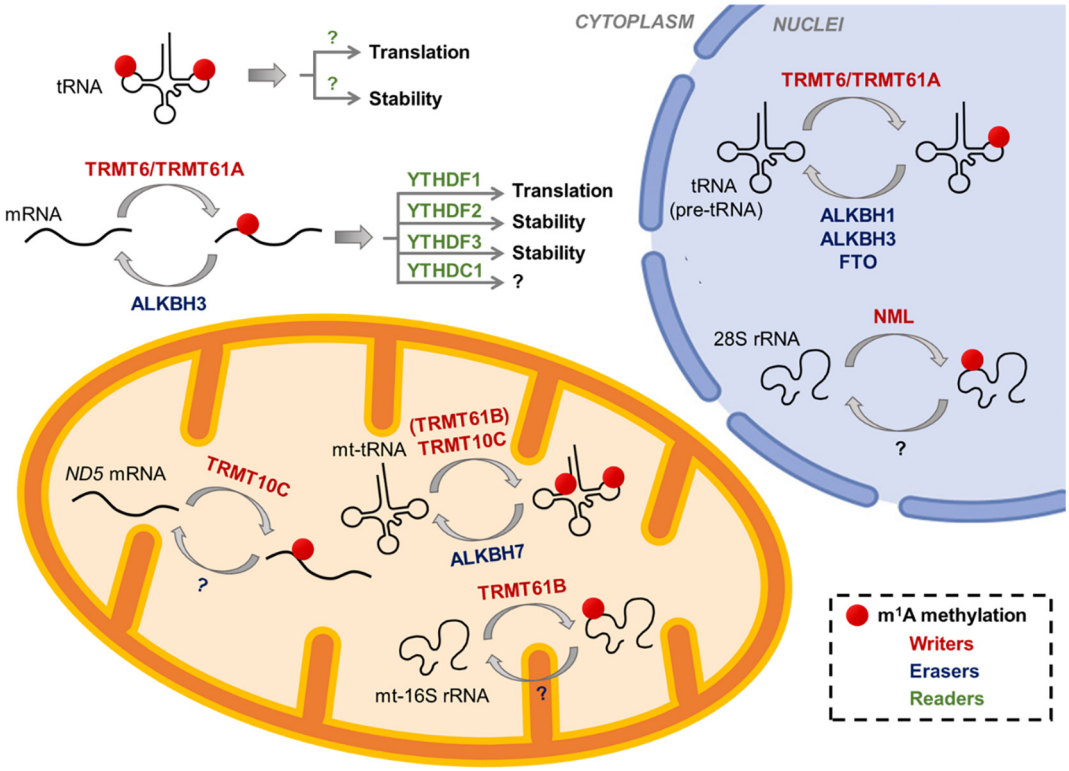

Fig. 2. M^1A modification of RNAs in mammalian cells.

suggesting that m^1A in mt-RNA regulates the nascent polycistronic mt-RNA processing.

2) Alteration of RNA structure: The distribution of m^1A in RNAs shows marked features, commonly around the GC-rich regions, such as the *T*-loop of tRNAs, within sequence GUUCNANNC in mRNAs [6,9], and around sequences HGGAGRA and/or WGGANGA (H = A, U, or C, R = G or A) in lncRNAs [7]. m^1A is considered to alter the secondary and tertiary structures of RNA via its positive charge [7,9]. It is worth noting that the GC-rich regions tend to form *T*-loop-like or hairpin structures within RNAs, which is almost invariable for the m^1A deposition. In addition, m^1A writer TRMT6/TRMT61A catalyzes m^1A at *T*-loop-like elements of RNA [24]. Therefore, m^1A is likely to play role in maintaining or stabilizing the *T*-loop-like structure, instead of changing the linear structure into a *T*-loop-like structure. The "loop" structure could be further strengthened by the presence of m^1A through its positive charge to impair Watson-Crick base pairing. In some cases, m^1A induces the correct folding of tRNAs. For instance, in mt-$tRNA^{Lys}$, m^1A9 shifts the dynamic equilibrium in favor of the cloverleaf structure and contributes to the correct formation of DHU loop [19,36]; in the initiator methionine tRNA ($tRNA^{iMet}$), m^1A58 maintains the tRNA-like structure for $tRNA^{iMet}$ through the unique A54–A58 interaction [29,40]. m^1A modification is likely an early maturation event for tRNA.

3) Regulation of translation: The m^1A can affect both the initiation and elongation process of translation via modifications in tRNA, mRNA and rRNA. The regulatory effects on translation depend on the deposition of its targets. **i) tRNA**: m^1A modification in either tRNA or mt-tRNA shows a positive role in translation. For instance, overexpression of m^1A erasers ALKBH1, ALKBH3 or FTO significantly suppresses the translation initiation and translation efficiency [15,33,41–42]. On one hand, m^1A58 stabilizes $tRNA^{iMet}$ to enhance the translation initiation, and ALKBH1-catalyzed demethylation attenuated the translation initiation [15,29]. On the other hand, the m^1A-modified tRNAs are preferentially recruited to active polysomes to promote translation [15]. In mt-tRNA, m^1A modifications in mt-tRNAs promote the translation of mitochondrial transcripts [43]. For instance, the level of m^1A58 in mt-$tRNA^{Lys}$ strongly increases protein synthesis [44]. **ii) mRNA**: The modifications of m^1A have diversified effects on protein synthesis. m^1A located in 5′UTR of mRNA is associated with increased translation initiation and translation efficiency [9]. m^1A can disrupt RNA base-pairing and induce local RNA duplex melting, which destabilizes the secondary structure in the 5′ UTR to promote the initiation step [45]. In contrast, m^1A in the CDS of both mRNA and mt-mRNA interferes with translation [6,24,32]. The inhibitory effect of m^1A within the CDS is probably through a mechanism involving ribosomal scanning or the binding of releasing factor to modulate translation [45]. Our recent study revealed that knockdown of ALKBH3 can increase the binding between *ATP5D* mRNA and eRF1, which resulted in enhanced termination efficiency [38]. **iii) rRNA**: m^1A in rRNA is likely associated with the proper formation of the 80S initiation complex. Lacking yeast m^1A methylase Rrp8 causes the incompetent loading of the 60S on the 43S-preinitiation complex, which may be due to the conformational alteration of 25S rRNA in the absence of m^1A645 [37].

4) Regulation of RNA stability: The presence of m^1A might be involved in the structural thermostability of tRNAs. In yeast and mammals, tRNA m^1A58 is a major modification and is critical for the stability of $tRNA^{iMet}$. ALKBH1 deficiency improves the cellular level of $tRNA^{iMet}$ by stabilizing $tRNA^{iMet}$ [15]; hypomodified $tRNA^{iMet}$ can be polyadenylated and then degraded by exonuclease Rex1p and exosome in yeast [46]. On the contrary, deficiency of m^1A writers has the possibility of inducing thermo-sensitivity of tRNAs [8]; knockdown of ALKBH1 fails to rescue tRNA from cleavage [47]; overexpression of ALKBH3 induces the formation of tRNA fragments (tRFs) [27]. It is reported that m^1A together with other post-transcriptional modifications can enhance the melting temperature of tRNAs [48]. Interestingly, certain nucleotide modifications including m^1A can be induced at high temperatures, and the biosynthesis of these modifications confers significant thermal stabilization to thus modified tRNAs [48]. However, m^1A58 in the mt-$tRNA^{Leu(UUR)}$ does not appear to affect its stability [44]. In mitochondrial 16S rRNA, m^1A947 is likely to stabilize it [22]. Besides, m^1A is associated with the mRNA destabilization mediated by reader proteins YTHDF2 and YTHDF3 [49–51]. Together, the regulation of m^1A in the stability of RNA is far better studied. It is likely that m^1A plays a critical role in the stabilization of tRNAs, but its effect on the stabilization of other RNAs such as mt-tRNA and mRNA remains to be elucidated.

In the nucleus, m^1A modifications in pre-tRNA (as well as tRNA) and 28S rRNA are installed by m^1A writers TRMT6/TRMT61A and NML, respectively. m^1A-modified tRNA can be removed by erasers ALKBH1, ALKBH3 and FTO. In the mitochondrion, mt-tRNA and a subset of mt-mRNA are methylated by TRMT10C. TRMT61B methylates mt-16S rRNA and possibly mt-tRNA. m1A in mt-tRNA is erased by ALKBH7. mt, mitochondrial. In the cytoplasm, mRNA is methylated by TRMT6/TRMT61A and demethylated by ALKBH3. m^1A readers recognize m^1A and execute specific functions.

3. Modulation of m^1A modification in cancer biology

m^1A is associated with diverse cellular functions. Dysregulation of m^1A leads to diseases such as tumorigenesis, cardiovascular diseases, pulmonary diseases and Alzheimer's disease [52–54]. Herein, the roles of m^1A in cancer biology are summarized Table 2.

1) Proliferation: m^1A regulators including TRMT6, TRMT61A and ALKBH3 have been found to promote the proliferation of cancer cells from gastrointestinal cancer (GI) [55–56], hepatocellular carcinoma (HCC) [57], glioma [58], prostate cancer [41,59], and colorectal cancer (CRC) [60]. In GI, HCC and glioma, both m^1A regulators and m^1A-modified mRNAs can modulate the PI3K/AKT pathway to promote the proliferation of cancer cells [56–57,61]. In addition to mRNA, m^1A can promote proliferation via the regulation of tRNAs. For instance, TRMT6/TRMT61A-elevated m^1A58 $tRNA^{iMet}$ promotes the proliferation and malignant transformation of glioma [58]; ALKBH3 promotes cell proliferation through enhancing protein synthesis by demethylation of tRNA in prostate cancer [41]. Remarkably, our recent study shows that ALKBH3 can generate tRNA-derived small RNAs (tDRs) via demethylation of m^1A-tRNA, which further promotes cancer cell proliferation and invasion [27].

2) Invasion: Only a few studies have reported the regulation of m^1A on cell invasion. In ovarian and breast cancers, ALKBH3 induces the increased m^1A-modified *CSF-1* mRNA to improve its translation initiation and cancer cell invasiveness [51]; ALKBH3 can also promote cancer cell invasion via destabilizing tRNAs [27]. YTHDF3, acting as m^1A reader, is found to suppress the invasion and migration of trophoblast, via promoting the mRNA decay of *IGF1R* [50].

3) Cell metabolism: In HCC, TRMT6/TRMT61A elevates a subset of m^1A-tRNA to increase PPARδ translation, resulting in the stimulation of cholesterol synthesis to promote the oncogenesis of HCC [62]. Our recent study reveals that ALKBH3 promotes the glycolysis of cancer cells by modulating the expression of m^1A-modified *ATP5D* mRNA [38]. In addition, ALKBH7 is found to regulate obesity by facilitating the utilization of short-chain fatty acids [63]. However, whether m^1A modification is involved in the ALKBH7-mediated regulation of obesity remains to be elucidated.

4) Senescence and cell death: m^1A might likely play role in the regulation of cellular senescence and cancer cell death, since

Table 2
Regulation of m^1A modifications in cancer biology.

Biological function	m^1A regulator	RNA target	Effect	Cancer/ Cell type	Mechanism
Proliferation	TRMT6, TRMT61A, ALKBH3	mRNA	Promotion	GI, HCC, Glioma	Modulation of PI3K/AKT pathway [56–57,61]
	TRMT6, TRMT61A	$tRNA^{iMet}$	Promotion	Glioma	Upregulation of m [1]A58 in $tRNA^{iMet}$ [58]
	ALKBH3	tRNA	Promotion	PAAD, OC	Enhancing protein synthesis by demethylating tRNA [41]
					Generation of tRNA-derived small RNAs by demethylating tRNA [27]
Invasion	ALKBH3	mRNA	Promotion	BC, OC	Promoting translation of m^1A-modified *CSF-1* mRNA [51]
	ALKBH3	tRNA	Promotion	PAAD, OC	Generation of tRNA-derived small RNAs by demethylating tRNA [27]
	YTHDF3	mRNA	Suppression	Trophoblast	Promoting the mRNA decay of *IGF1R* mRNA [50]
Cancer metabolism	TRMT6, TRMT61A	tRNA	Promotion	HCC	Increasing PPARδ translation to stimulate cholesterol synthesis [62]
	ALKBH3, YTHDF1	mRNA	Promotion	OC	Increasing expression of *ATP5D* mRNA to promote the glycolysis [38]
Senescence, cell death	ALKBH3	mRNA	Promotion	NSCLC, BLCA	Increasing the expression of p27 and p21 [65–66].
Tumor microenvironment	YTHDF3	mRNA	Promotion	RAW264.7	Regulating the macrophage M1 and M2 polarization [70],

ALKBH3 has been reported to regulate the cell cycle [64]. Knockdown of ALKBH3 results in the senescence induction and cell cycle arrest in lung cancer and urothelial carcinomas, by increasing the expression of cell cycle arrest proteins p27 and p21, and modulating NADPH oxidase and tweak/Fn14/VEGF signals [65–66]. However, whether ALKBH3 mediates this function as an RNA or DNA methyltransferase was not elucidated.

5) Tumor microenvironment (TME): Studies shows that m^1A modification is critical to the shaping of immune microenvironment and the formation of TME complexity. In ovarian cancer (OC), colon cancer (CC), HCC and oral squamous cell carcinoma (OSCC), m^1A regulators and m^1A modification patterns correspond to the ever-changing immune microenvironment during cancer development [60,67–69]. The m^1A-related phenotypes are correlated to the immune cell infiltration in TME, where different m^1A patterns are identified in immune-desert, immune-inflamed and immune-excluded phenotypes [60,67]. In addition, eight m^1A regulators are positively correlated with activated mast cells, plasma cells and M1 macrophages in abdominal aortic aneurysm (AAA). Among them, YTHDF3 promotes macrophage M1 polarization but inhibits macrophage M2 polarization [70].

Increasing evidence highlights the important role of m^1A modification in the tumorigenesis of various cancers. Remarkably, some of these correlations might be due to the downstream effects or "side effects" of the global manipulation of m^1A-related regulators. To avoid such interference, site-specific manipulation of m^1A meets the urgent needs of m^1A methylation study. However, only two programmable m^1A tools have been reported [38,71] and their usage in functional study remains to be popularized.

4. m^1A modification as a potential diagnostic and therapeutic target

The relevance between m^1A modifications and cancer progression and prognosis has been of attention recently. Increasing reports suggest that the levels of m^1A methylation, m^1A-related regulators, as well as the m^1A-related RNAs might be novel biomarkers for cancer prognosis. In addition, modulating the m^1A-related regulators and/or m^1A modification on transcripts is likely becoming a breakthrough in cancer therapies.

1) Targeting m^1A methylation for cancer prognosis:

i) Total m^1A level: Level of m^1A can be detected in spontaneous urine samples. Zheng et al., first reported that the m^1A content in CRC patients is higher than that in healthy controls. And m^1A levels are positively associated with the Duke stage for CRC [72]. Later, m^1AScore is generated to quantify the individual patient's m^1A modification pattern. In CC and OSCC, patients with a high m^1AScore show more lymphatic invasion, shorten survival and worse response after immunotherapy [60,68]. However, a high m^1AScore in OC patients is usually accompanied by a better survival advantage, a lower mutational load and marked therapeutic benefits from chemotherapy and immunotherapy [67]. The m^1A level shows the potential predictive ability for the prognosis of cancers, but the relevance between m^1A level and cancer progression and/or prognosis is likely related to tumor species.

ii) m^1A-related regulators: m^1A-related regulators are commonly high expressed in multiple cancers. Among them, m^1A writer TRMT6, TRMT61A and eraser ALKBH3 are associated with poorer prognosis in a variety of cancers [41,51,56–57,59–61,65,66,73,74]. Expression of TRMT61B and TRMT10C, which are m^1A writers for mitochondrial RNAs, could be used as an independent risk factor for the prognosis of gastric cancer and HCC, respectively [55,57,75]. ALKBH7, which is high expression in 17 cancers and low expression in 5 cancers compared to paired normal tissues, might be a potential biomarker for pan-cancer prognosis and prediction of therapeutic outcomes [76]. Remarkably, ALKBH1 is the only m^1A regulator that is related to the good prognosis of patients with pancreatic cancer (PAAD) [77]. In glioblastoma, ALKBH1 expression of patients is not associated with overall survival rates [78]. For FTO, YTHDF1, YTHDF2, YTHDF3 and YTHDC1, high expression of them is closely associated with poor clinical outcomes in both CRC and HCC [57,60,79]. However, all of them are not restricted in the regulation of m^1A, but also m^6A and other modifications. Therefore, their prognostic potential may be associated with m^6A as well.

iii) m^1A-related RNAs: m^1A-related RNAs might become effective prognostic predictors for cancer diagnosis. On one hand, Zheng et al., reveal that m^1A-regulating genes are correlated with advanced clinical stages and poor prognosis of PAAD [77]. On the other hand, tRFs derived from m^1A-regulated tRNAs are correlated with the dysregulation of TRMT6/61A expression, and long 3′ tRFs are highly enriched in bladder cancer [80]. Our study further confirms that the plasma level of 5′-tRF-GlyGCC acts as a novel biomarker for colorectal cancer diagnosis [81].

2) m^1A modification for cancer therapy.

i) Inhibitors targeting m^1A-related regulators: Due to the positive roles of m^1A-related regulators in tumorigenesis, developing selective inhibitors targeting m^1A-related regulators is one of the efficient ways for cancer therapy. So far, inhibitors targeting TRMT6/TRMT61A, ALBKH3 and FTO are reported (Table 3). For TRMT6/TRMT61A, thiram (tetramethyl thiuram disulfide) is recently identified as a potential candidate compound that selectively inhibits the interaction between TRMT6 and TRMT61A. Thiram treatment suppresses the self-renewal of HCC cells *in vitro* and also decreases tumor growth *in vivo* [62]. However, thiram was approached by FDA as an antimicrobial drug and shows liver damage in chickens at high doses [82]. The pre-clinical investigation of HCC therapy needs further evaluation. For ALKBH3, HUHS015 and

Table 3
Inhibitors targeting m^{1}A-related regulators.

Target	Compound	Mechanism	Effect on cancer
TRMT6/ TRMT61A	Thiram	Inhibits TRMT6-TRMT61A interaction	HCC: Suppress self-renewal and tumor growth [62]
ALKBH3	HUHS015/ Compound 7I	Suppress ALKBH3 activity	PC: Inhibit proliferation of DU145 cells [83–84]
FTO	18077/18097	Bind to the active site of FTO	BC: Inhibited cell cycle process and migration of cancer cells [86]
	CHTB	Bind to a novel site of FTO and inhibit demethylase activity [89]	–
	CS1/CS2	Block the catalytic pocket of FTO	AML: Inhibits cancer cell proliferation, cancer stem cell self-renewal and immune evasion [90]
	Dac51	Suppress FTO activity	Melanoma: Promotes T cell response and enhances the anti-PD-1 therapy [91]
	Entacapone	Compete with the catalytic site of FTO	HCC: Interfere with gluconeogenesis through FOXO1 [92]
	FB23/FB23-2	Directly bind to FTO and inhibit demethylase activity	AML: Suppress proliferation and promote differentiation/apoptosis [93].
	FTO-04	Block the catalytic activity of FTO	GBM: Prevents neurosphere formation and self-Renewal [94].
	N-CDPCB	Competitive bind to a novel site of FTO and inhibit demethylase activity [95]	–
	MA/MA2	Inhibition of the catalytic activity of FTO	GBM: Inhibit GSC cell growth and self-renewal [88]
	MO-I-500	Inhibition of the catalytic activity of FTO	BC: Inhibit cell survival via decreasing FTO and IRX3 proteins [96]
	R-2HG	Suppress FTO activity	AML, GBM: Inhibit proliferation/survival of FTO-high cancer cells [97]
	Rhein	Competitive bind to FTO catalytic domain	AML: Prevent or override tyrosine kinase inhibitor resistance [98] BC: Decrease tumor growth [99]
	Saikosaponin-d	Occupy the substrate-binding site of FTO	AML: suppress cell proliferation, promote apoptosis/cell-cycle arrest [100]

its derivative Compound 7I (1-(5-fluoro-1H-benzimidazol-2-yl)-3-methyl-4-phenyl-1H-pyrazol-5-ol) are evaluated as prostate cancer antigen-1 (PCA-1/ALKBH3) inhibitors. Compound 7I shows potent antiproliferative effects on DU145 cells *in vivo* [83–84]. For FTO, as the first discovered RNA methylase, over ten FTO-targeted small molecule inhibitors are developed, including Rhein, CHTB, *N*-CDPCB, Meclofenamic acid 2 (MA2), R-2-hydroxyglutarate (R-2HG), FB23-2, CS1, CS2, 18,077 and 18,097 [85–86]. Among them, seven FTO inhibitors, MA2, R-2HG, FB23-2, CS1, CS2, 18,077 and 18,097 show anti-cancer effects both *in vitro* and *in vivo*. MA2, which can bind at the surface area of the FTO active site, is an FDA-approved nonsteroidal anti-inflammatory drug (NSAID) [87]. MA2 shows an inhibitory effect on tumor growth in glioblastoma-bearing mice [88], which likely becomes the most potent small molecule FTO inhibitor for anti-tumor therapy.

ii) Editing m^{1}A-modified RNAs: m^{1}A modification on target RNA regulates its expression. Therefore, targeted editing of m^{1}A in specific RNA becomes a possible approach for cancer therapy. CRISPR proteins recognizing RNA as substrates, such as Cas13 and CasRx, are powerful tools to establish editing systems targeting RNA modification. Xie et al., developed a targeted m^{1}A demethylation tool called "REMOVER" via combining the RNA-targeting capability of dCasRx (catalytically inactive RNA-targeting RfxCas13d enzyme) and m^{1}A eraser ALKBH3. "REMOVER" can demethylate m^{1}A of specific RNA such as *MALAT1* and modulate their stability[71]. However, no further application of "REMOVER" has been reported yet. Recently, we establish a targeted m^{1}A demethylation system "dm^{1}ACRISPR" by fusing PspCas13b with ALKBH3 [38], which was based on our previous method to demethylase m^{6}A [101]. Targeted demethylation of m^{1}A in *ATP5D* mRNA, which is a key regulator for glycolysis, by "dm^{1}ACRISPR" significantly suppresses the energy metabolism and tumorigenesis of cancer cells [38], indicating the possibility of novel cancer therapy via modulating specific m^{1}A modification. Similar to CRISPR/Cas9 which has shown great progress and potential in tumor therapy, site-specific manipulation strategy on m^{1}A exhibits anticipated potential as well. In addition, the m^{1}A modification pattern is closely associated with the immune cell infiltration in TME. Therefore, combining the targeting m^{1}A-editing and immune response therapy such as PD-L1, might be another promising approach for cancer therapy in the future.

5. Challenges and perspectives

m^{1}A methylation is one of the most prevalent modifications that are highly conserved in both eukaryotic and prokaryotic RNAs, suggesting its critical role in living body. Maintaining the structure/folding of RNA is considered to be the most important function of m^{1}A, especially in tRNAs that regulate protein biosynthesis. There are over 90 modifications in tRNAs, and about 13 modifications per tRNA are presented on average [8,102]. Modifications in tRNA greatly limit the functional study of one particular modification in tRNAs. Therefore, whether m^{1}A would cooperate with other modifications in tRNA to shape the tRNA folding, whether there are other unrevealed m^{1}A sites in tRNA, and what the exact function of m^{1}A in tRNAs are questions that need to be elucidated. In addition to tRNA, m^{1}A is presented in a low number of mRNAs, typically at low stoichiometries. The low stoichiometry of m^{1}A has important implications for how m^{1}A could affect mRNA. It is commonly believed that m^{1}A regulates the expression of targets, and it acts as a gene expression regulation mechanism in response to changes in the external environment. However, this is worth thinking about the impact of m^{1}A, which with low stoichiometry in mRNAs, on the regulation of target expression.

Despite the to-be-elucidated function of m^{1}A on RNAs, the regulatory effects of m^{1}A in cancer development have been confirmed in the past decade. It is confirmed that the m^{1}A level, m^{1}A modification pattern, and the expression of m^{1}A-related regulators are closely associated with tumorigenesis. Therefore, it is promising to target m^{1}A and its regulators for cancer diagnosis and therapies. Targeting epigenetic modification is a new and challenging development direction for cancer diagnosis and therapy. For instance, there is no epigenetic drug targeting RNA modification has been approached currently, although thousands of candidates are under clinical evaluation. So far, there are twelve potential chemicals targeting m^{1}A-related regulators that show suppressive effects on cancer cells, meaning that the anti-cancer drugs targeting m^{1}A are still in the initial stage of research. In addition to small molecule inhibitors, targeted m^{1}A editing is a novel approach to cancer therapy. CRISPR/Cas9 system is a powerful tool for genetic disease treatments. Similar to CRISPR/Cas9, RNA-targeting CRISPR shows great capability in transcript editing, with further advantages such

as no DNA mutation inheritance caused by the off-target effect. However, challenges about CRISPR delivery and its editing effect in solid tumors remain to be solved.

6. Conclusions

In this review, we summarized the functions and the modulation of m^1A modification in cancer biology. Acting as one of the most abundant internal modifications of RNAs, the specific biological functions of m^1A modification in RNAs, including tRNA, rRNA, mRNA and lncRNA, remains largely unknown. Increasing evidence suggests a critical role of m^1A modification in cancer development. On one hand, m^1A-related regulators can modulate the progression of cancers; on the other hand, m^1A level and/or m^1A-related regulators might be novel biomarkers or therapeutic targets for cancers. A full understanding of the mechanism underlying m^1A modification is distant. However, with the in-depth study of m^1A modification, including its functions and association with cancer progression, targeting m^1A modification might provide new potential options for both cancer diagnosis and treatment.

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CRediT authorship contribution statement

Jiexin Li: Conceptualization, Investigation, Writing – original draft. **Haisheng Zhang:** Investigation, Writing – original draft. **Hongsheng Wang:** Conceptualization, Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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