Latest Progress on RNA Methylation Modification in Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the most common malignant tumor worldwide, characterized by insidious onset as well as high incidence, recurrence, metastasis, and mortality rates. At present, there is no effective clinical treatment method except transplantation. The emergence and development of high throughput sequencing technologies in recent years has turned the epigenetics of cancer to spotlight; specifically, RNA methylation modification becomes a much discussed topic recently. RNA methylation modification plays a key role in the occurrence and development of HCC. This article reviews the relationship between different types of RNA methylation modification and HCC progression, which provides a new research direction for exploring the pathogenesis of HCC and developing new diagnostic methods and therapeutic targets.

Keywords: RNA modification, RNA methylation, Hepatocellular carcinoma

1 Introduction

RNA modification occurs at the post-transcriptional level. To date, many studies have shown the existence of at least 150 kinds of methylation modifications to different types of RNAs, such as messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), and various non-coding RNAs. RNA methylation modifications, which represent one of the most extensively studied type of modifications, include N6-methyladenosine (m6A), 5-methylcytosine (m5C), N1-methyadenosine (m1A) modification, and others that occur during mRNA processing. Proteases related to RNA modification, such as methylases, demethylases, and methylation-binding proteins, play an important role. Our understanding on RNA methylation modification opens up a new area of research that investigates the post-transcriptional modulation mechanism in eukaryotes. The roles of different types of RNA methylation modifications in hepatocellular carcinoma (HCC) are summarized below.

2 m6A modification of mRNA in HCC

m6A modification occurs at the N6 sites of RNA adenosine, and most of m6A residues are in the last exons for 3'-UTR regulation[1]. It is the most extensive, stable, and conservative mRNA modification in eukaryotes.
Studies have found that methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), methyltransferase-like 16 (METTL16), Wilms’ tumor 1-associating protein (WTAP), zinc finger CCCH domain-containing protein 13 (ZC3H13), and RNA-binding motif protein 15 (RBM15) are the methyltransferase-like enzymes responsible for m\(\text{6A}\) modification in mammals. On the contrary, m\(\text{6A}\) can be eliminated by demethylases, such as fat mass and obesity-associated protein (FTO) and alkB homolog 5 (ALKBH5). m\(\text{6A}\) modification is recognized by proteins of YTH domain family 1/2/3 (YTHDF1/2/3), YTH domain-containing proteins 1/2 (YTHDC1/2), and heterogeneous nuclear ribonucleoproteins C (HNRNPC), leading to the initiation of downstream signals\[^2\]. The proteases involved in m\(\text{6A}\) modification play vital roles in the initiation and progression of HCC by targeting a variety of tumor-related genes (Figure 1). For example, a recent study based on The Cancer Genome Atlas found that eleven genes related to m\(\text{6A}\) methylation, such as METTL3, YTHDF1, YTHDF2, and FTO, were abnormally expressed in HCC, and five of these genes are independent potential predictors of HCC, indicating that m\(\text{6A}\) methylation-related genes might be promising prognostic indicators or therapeutic targets of HCC\[^3\].

### 2.1 Methylases

METTL3, an RNA methylase for m\(\text{6A}\) modification, plays an important biological role in embryonic development and cancer, such as the control of cell proliferation and differentiation. A previous study reported that METTL3 was significantly up-regulated in HCC at both RNA and protein levels, its down-regulation mediated by siRNA and 2-deoxyglucose (2-DG), a glycolytic inhibitor, had a synergistic inhibitory effect on tumor

**Figure 1.** Implications of m\(\text{6A}\)-dependent methylation modification on signaling pathways and bioprocess involved in HCC carcinogenesis. Abbreviations: METTL3, methyltransferase-like 3; 2-DG, 2-deoxyglucose; PDK4, pyruvate dehydrogenase kinase 4; RDM1, RAD52 motif 1; UBC9, ubiquitin-conjugating enzyme 9; SUMO1, small ubiquitin-like modifiers 1; EMT, epithelial-mesenchymal transformation; WTAP, Wilms’ tumor 1-associating protein; ETS1, ETS proto-oncogene 1; FTO, fat mass and obesity-associated protein; PKM2, pyruvate kinase M2; HIF-2\(\alpha\), hypoxia inducible factor 2\(\alpha\); YTHDF1, YTH domain family 1; YTHDF2, YTH domain family 2; IL11, interleukin 11; SERPINE2, serpin family E member 2.
growth *in vitro*[^41]. Moreover, METTL3 is closely related to glycolysis regulation. Through binding with YTHDF1/eEF-2 complex and IGF2BP3, m^6^A-modified pyruvate dehydrogenase kinase 4 (PDK4) was found to promote glycolysis in HCC, suggesting an oncogenic effect of m^6^A/PDK4 on HCC[^5]. The aforementioned findings suggest that inhibition of glycolysis by down-regulating the expression of m^6^A in HCC might represent a potentially effective anti-HCC strategy. In addition, up-regulated expression METTL3 and its carcinogenic function in HCC have also been reported. Specifically, the expression of RAD52 motif 1 (RDM1), a key factor for DNA repair and recombinant which contains anti-tumor activity, was inhibited due to m^6^A modification of RDM1 mRNA as a result of METTL3 overexpression in HCC tissues, leading to accelerated growth and pathologic changes of HCC[^6]. Another study found that the upregulation of METTL3 would increase the m^6^A expression, thus promoting the migration, invasion, and epithelial-mesenchymal transformation (EMT) of HCC tumor cells *in vitro and in vivo*[^7]. These studies suggested that the upregulation of METTL3 expression is an independent prognostic factor for HCC. In addition, Xu *et al.* showed that METTL3 modified by a small ubiquitin-like modifier SUMO1 promoted the development of HCC tumor by regulating snail mRNA homeostasis, revealing a novel mechanism underlying the regulation of m^6^A modification in HCC progression[^9].

Therefore, METTL3 is an invaluable therapeutic target of HCC, which has been utilized for devising new therapeutic approaches. By stabilizing m^6^A modification, overexpression of METTL3 led to the upregulation of long non-coding RNA (lncRNA) LINC00958, which aggravated the malignant phenotypes of HCC, and a drug delivery system containing LINC00958 siRNA presented good anti-tumor efficacy after administration[^9]. In addition to METTL3, METTL14 has been shown to play an important role in promoting the proliferation and migration of HCC cells and also might have many other unknown roles[^10]. A recent study that underscored the functional relevance of other factors in HCC has reported that WTAP regulated the post-transcriptional inhibition of ETS proto-oncogene 1 (ETS1) by regulating m^6^A modification, thereby promoting the development of HCC tumor cells in the G2/M phase[^11]. This suggests that WTAP may be a potential therapeutic target for HCC.

### 2.2 Demethylases

The loss of demethylase FTO was clinically correlated with HCC progression, as evidenced by increased AFP level, tumor size, metastasis, and vascular invasion, as well as poor prognosis. As such, FTO might be used as a new biomarker for HCC[^12]. A mechanistic study demonstrated that FTO knockout induced G0/G1 phase arrest in HCC cells and FTO induced pyruvate kinase M2 (PKM2) demethylation to accelerate the protein translation process, thus promoting the occurrence of HCC[^13]. Unlike in HCC, a carcinogenic role of FTO was also noted in other different types of cancer. For instance, overexpression of FTO promotes the occurrence of leukemia, breast cancer, gastric cancer, endometrial cancer, etc.[^14]. It has been found that R-2-hydroxyglutaric acid (R-2HG) inhibits the proliferation and metastasis leukemia cells by inhibiting FTO activity[^15]. As the loss of FTO was clinically correlated with HCC progression, further studies are required to address whether FTO is a crucial factor in the treatment of HCC, which may be significant for identification the importance of m^6^A modification in HCC.

The role of ALKBH5 in HCC has not been widely studied. Recently, we found that ALKBH5 suppressed the tumorigenesis of pancreatic cancer by repressing methylation modification of Wnt inhibitory factor 1 (WIF-1) that inhibits the Wnt pathways, and silence ALKBH5 could increase the proliferation, migration, and invasion of pancreatic ductal adenocarcinoma (PDAC) cells[^16]. Furthermore, lower level of ALKBH5 was also clinically related to poorer prognosis of PDAC and other cancers. Thus, we believe that ALKBH5 may be a promising therapeutic target for cancers, including HCC[^16].

### 2.3 Methylated DNA binding proteins

YTHDF1 and YTHDF2 are methylated DNA binding proteins that mediate the degradation
of mRNA by identifying the modification sites of m6A[17]. Both YTHDF1 and YTHDF2 were highly expressed in HCC and critically involved in HCC progression; therefore, they have prognostic values[18-20]. A previous study has found that silencing YTHDF2 in HCC cells could cause inflammation and vascular remodeling and promote the metastasis of HCC[21]. YTHDF2-mediated m6A modification and resultant HCC growth inhibition could be restored when PT2385, a hypoxia-inducible factor 2α antagonist, was administered. Moreover, YTHDF2 overexpression in HCC could promote the degradation of EGFR mRNA by recognizing and binding to the modification site of EGFR mRNA 3'-UTR, thus playing a role in inhibiting the proliferation and growth of HCC tumor cells[22]. In addition, the expression level of microRNA-145, which could regulate its methylation level by targeting the 3'-UTR region of YTHDF2 protein, was negatively correlated with YTHDF2 in HCC; therefore, microRNA-145 could regulate the malignancy of HCC and might be a potential therapeutic target for HCC[23].

The regulation of m6A modification of dendritic cells in the process of antigen cross-presentation and the anti-tumor immune response of CD8+ T cells by YTHDF1 suggests that YTHDF1 could be used as a potential therapeutic target for anticancer immunotherapy[24]. Whether YTHDF1 could play an anti-tumor role in HCC remains unclear, and the specific mechanism of action remains to be elucidated.

3 m5C modification of mRNA in HCC

The 5-methylcytosine (m5C) modification of RNA mainly happens at tRNAs and rRNAs, while m5A is more frequently detected in mRNAs[25]. A previous study found that m5C modification is enriched in CG-rich regions and downstream part of the translation start sites, and this type of modification has conservative, specific, and dynamic characteristics in the post-transcriptional modification of mammalian RNA[26]. The NOL1/NOP2/SUN domain family member 2 (NSUN2) methyltransferase is the main enzyme that catalyzes the formation of m5C, and Aly/REF export factor (ALYREF, an mRNA transport adapter) functions as a specific mRNA m5C-binding protein that regulates mRNA export. m5C modification could promote mRNA expression under the combined action of NSUN2 and ALYREF. The distribution patterns of m5C are different in HCC and adjacent non-tumor tissues. The m5C modification was significantly enriched at the translational start codon of mRNA of HCC, while the enrichment of m5C at 3'-UTR was decreased, suggesting the functional differences of m5C between tumor cells and normal liver cells[27]. Further studies on the role of proteases in m5C modification found that highly expressed NSUN2 and ALYREF were associated with patient survival outcomes and were independent prognostic markers for HCC[25]. Among them, NSUN2 regulated methylation and demethylation, while ALYREF regulated the cell cycle and mitosis of HCC tumor cells[25]. These findings show that m5C plays a crucial role in the progression of HCC. Further studies are warranted to explore the mechanism of action of m5C in HCC progression so as to provide a new perspective for targeted therapy of HCC.

4 Non-coding RNA methylation in HCC

Non-coding RNA refers to RNA without protein-coding potential, including rRNA, tRNA, microRNA, and lncRNA. Although these RNAs do not code for any proteins, they can perform their respective biological functions at the RNA level. Given the fact that the abnormal methylation of the non-coding RNA can influence the occurrence and development of HCC and affect its drug resistance, they may be regarded as potential therapeutic target and prognostic marker for HCC[28].

4.1 m5A modification of tRNA

tRNA is unique among all RNA types and has the widest range of modification types. The N1-Methyladenosine (m5A) modification was first discovered in tRNA in 1961, and high-throughput sequencing analysis revealed that m5A modification was crucial for regulating the stability of tRNA[29]. The high enrichment of m5A at 5'-UTR of the mRNA could improve translation efficiency. Demethylases such as ALKBH1 and ALKBH3 could reverse the modification of m5A, resulting in reduced translation and protein
synthesis\textsuperscript{30}. Moreover, $m^1A$ was reported to be ubiquitously detected in mitochondrial encoded transcripts, suggesting that $m^1A$ modification in mitochondrial mRNA could also interfere with translation\textsuperscript{31}. Liu et al. found that ALKBH3 was highly expressed in HCC, and its expression was related to tumor differentiation and TNM stage\textsuperscript{32}. Inhibition of ALKBH3 expression would make HCC cells stay in the G1 phase through P21/P27 mediation, thereby inhibiting the proliferation of HCC cells \textit{in vitro} and the formation of metastatic tumors \textit{in vivo}. These results suggest that ALKBH3 might be a potential therapeutic target for HCC. At present, a line of evidence shows that ALKBH1, as a $m^1A$-modified demethylase, could directly affect the translation initiation by regulating initiator methionine tRNA (Met-tRNA$^\text{Met}$) and the translation elongation by regulating the methylation of target tRNA\textsuperscript{33}. Nevertheless, the regulatory process of tRNA modification in HCC is still unclear. A research extension to gain deeper insights would broaden our understanding of the epigenetic aspect of HCC.

4.2 Methylation modification of rRNA

The ribosome is usually stabilized by rRNA through a variety of modifications that aggregate at important ribosomal functional sites, thereby promoting efficient and accurate protein synthesis. It has been reported that the common modifications in rRNA are pseudouridylation and 2'-O-methylation (Nm) modifications regulated by H/ACA box snRNAs and C/D box snRNAs, respectively\textsuperscript{34}. In addition, human 18S rRNA $m^6A$ is mediated by methyltransferase composed of heterodimer complex METTL5-TRMT112, and 28S rRNA $m^6A$ by methyltransferase ZCCHC4 that is highly expressed in HCC. The significant reduction of the HCC tumor size in ZCCHC4-knockout xenograft mouse models\textsuperscript{35,36} indicates that $m^6A$ modification of rRNA has functional significance for protein translation and tumor biology, insinuating new research directions for the diagnosis and treatment of HCC.

4.3 Methylation modification of microRNA

MicroRNAs (miRNAs) are non-coding single-stranded RNA molecules with a length of about 22 nucleotides encoded by endogenous genes, which are widely found in eukaryotes. miRNA dysfunction is a common feature of human cancers. In recent years, the abnormal regulation of miRNA methylation in the context of HCC occurrence and development has attracted much attention. Through genetic screening, it was found that the selected miRNA promoter methylation sites could be used as biological markers for judging the overall survival (OS), vascular infiltration, pathological grade, and clinical stage of HCC patients\textsuperscript{37}. The expression of miRNA-200b in HCC was significantly down-regulated, mainly through extensive methylation of CpG sites in the promoter region of miRNA-200b that directly targets BMI1, so as to regulate the proliferation, colony formation, cell cycle progression, and invasion of HCC cells\textsuperscript{38,39}. In addition, miR-200b acted in concert with 5-fluorouracil to induce apoptosis of HCC tumor cells \textit{in vitro} and to suppress tumorigenesis \textit{in vivo}. MiR-941 was significantly down-regulated in HCC tissues and cell lines, and miR-941 negatively regulated lysine (K)-specific demethylase 6B (KDM6B), a histone demethylase, through increased methylation to regulate the EMT process and the proliferation, migration and invasion of HCC cells\textsuperscript{40}.

The expression of miR-22 is down-regulated in HCC, influencing the expression of galectin-9 which is the downstream target of miR-22. Tri-methylation of H3K27 on the miR-22 promoter could promote the \textit{in vivo} and \textit{in vitro} expression of galectin-9, which has anti-tumor effects, thereby inhibiting the growth, metastasis, and invasion of liver cancer cells. Moreover, galectin-9 can be used as an immunosuppressant in the treatment of HCC\textsuperscript{41}. In HCC, the CpG island of miR-183 was highly methylated. Since the expression of mature miR-183 was negatively correlated with its methylation level, the abnormal hypermethylation of miR-183 could specifically promote the malignant transformation of HCC. MiR-183 might thus serve as a new diagnostic and prognostic marker\textsuperscript{42}. Similarly, miR-615-5p is hypermethylated and its expression is down-regulated in HCC, mainly due to the loss of KDM4B, thereby.
promoting HCC growth, metastasis, EMT, adhesion, and angiogenesis by inducing Ras-related protein RAB24\textsuperscript{[43]}. Furthermore, the expression of miR-142, which is a tumor suppressor in HCC, is often down-regulated due to hypermethylation\textsuperscript{[44]}. MiR-142 directly targets transforming growth factor-β (TGF-β), inducing tumor cell proliferation, endothelial cell transformation and angiogenesis, and finally leading to HCC malignancy. MiR-142 level was also related to HCC TNM stage, metastasis, and differentiation\textsuperscript{[44]}. Besides, hypermethylation of the miR-192-5p promoter might represent an important driving factor for the transformation of normal hepatocytes into liver cancer stem cells (LCSC), which is an indication of liver cancer occurrence\textsuperscript{[45]}. MiR-639 expression was down-regulated in HCC due to the hypermethylation at its promoter region, and critically involved in HCC growth, metastasis, and invasion\textsuperscript{[46]}. The expression of miRNA-145, which regulates the modification level of m^6A by targeting the 3'-UTR of YTHDF2 mRNA, was down-regulated in HCC, affecting the tumor growth process\textsuperscript{[23]}.

In general, hypermethylation and reduced expression of miRNAs are relatively common features in HCC. To date, a total of eight miRNAs, including has-mir-129-2, were found to be highly methylated in HCC, indicating that hypermethylation of miRNAs might be a new diagnostic and prognostic marker for HCC\textsuperscript{[47]}. The expression of chromosome 19 microRNA cluster (C19MC), the largest miRNA cluster in HCC, was upregulated due to hypomethylation of its promoter region\textsuperscript{[48]}. The aberrant level of C19MC was found to be positively correlated with the TNM stage of the tumor, whereas the miR-512-1, miR-516a-1, and miR-519a-1 of the cluster were negatively correlated with OS\textsuperscript{[48]}. Altogether, the methylation level of microRNA gene promoter might be negatively correlated with its expression level, and represented a potential diagnostic and therapeutic target for HCC (Table 1).

### 4.4 Methylation modification of LncRNAs

LncRNAs are non-coding RNAs larger than 200 nucleotides and lacking a specific complete open reading frame. LncRNAs are involved in the regulation of key signal pathways of HCC and affect the prognosis of patients. The overexpression of lnc-PDZD7, a potential oncogene, promoted HCC stem cell characteristics and abrogated tumor cell sensitivity to chemotherapeutic agents by regulating miR-101/EZH2/ATOH8 pathway, providing a new approach for clinical diagnosis and new therapeutic target for HCC\textsuperscript{[49]}. The methylation of lncRNA H19

<table>
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<th>microRNAs</th>
<th>Expression</th>
<th>Biological function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-200b</td>
<td>Down-regulated</td>
<td>Inhibition of cell proliferation, colony formation, cell cycle, and invasion</td>
<td>\textsuperscript{[37,38]}</td>
</tr>
<tr>
<td>miR-941</td>
<td>Down-regulated</td>
<td>Inhibition of cell proliferation, migration, invasion, and EMT</td>
<td>\textsuperscript{[39]}</td>
</tr>
<tr>
<td>miR-22</td>
<td>Down-regulated</td>
<td>Inhibition of cell growth, metastasis, and invasion</td>
<td>\textsuperscript{[40]}</td>
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<tr>
<td>miR-183</td>
<td>Down-regulated</td>
<td>Inhibition of cell growth</td>
<td>\textsuperscript{[41]}</td>
</tr>
<tr>
<td>miR-615-5p</td>
<td>Down-regulated</td>
<td>Inhibition of cell EMT, adhesion, and vasculogenic mimicry</td>
<td>\textsuperscript{[42]}</td>
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<tr>
<td>miR-142</td>
<td>Down-regulated</td>
<td>Inhibition of cell proliferation, EMT, and angiogenesis</td>
<td>\textsuperscript{[43]}</td>
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<tr>
<td>miR-192-5p</td>
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<td>Inhibition of cell growth</td>
<td>\textsuperscript{[44]}</td>
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<tr>
<td>miR-639</td>
<td>Down-regulated</td>
<td>Inhibition of cell growth, metastasis, and invasion</td>
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gene promoter led to its down-regulation in HCC, but its overexpression inhibited the proliferation and growth of HCC cells, thereby slowing down occurrence and development of HCC and increasing the sensitivity of HCC to chemotherapeutic drugs\cite{50}. Thus, targeting lncRNA H19 might provide promising insight into overcoming clinical chemoresistance.

LncRNA DLX6-AS1 was abnormally expressed in HCC, and silencing lncRNA DLX6-AS1 could inhibit the proliferation of HCC cells\cite{51}. In addition, the activation of STAT3 signal pathway and inhibition of the methylation of CADM1 promoter prevented the occurrence and development of liver cancer through inhibition of the stem cell characteristics of LCSC\cite{51}. LncRNA TCAM1P-004 and lncRNA RP11-598D14.1 were often down-regulated in HCC, and the EZH-mediated H3K27me3 trimethylation of their promoters could regulate the growth and transformation of HCC cells in vitro and tumor formation in vivo, suggesting that EZH2 is a very important regulatory factor and might be a potential therapeutic target for HCC\cite{52}. As a newly identified lncRNA molecule, LINC00662 not only plays an important regulatory role in gastrointestinal tumors but also regulates methionine adenosyltransferase 1A (MAT1A) and s-adenosylhomocysteine hydrolase (AHCY) by mediating the interaction between RNA and RNA or protein\cite{53}. Therefore, changing the methylation status of the LINC00662 promoter region could regulate the genes related to the occurrence and development of HCC\cite{51}.

LncRNAs may also regulate the biological characteristics of miRNAs by mediating abnormal methylation in its promoter region. The up-regulation of lncRNA PCAT-14 expression in HCC inhibits the expression of miR-372 by inducing the methylation of miR-372 promoter, thereby promoting the proliferation, invasion, and cell cycle progression of HCC cells. In addition, the expression of lncRNA PCAT-14 is related to the metastasis, tumor size, and TNM stage of HCC, and hence, could be used as a new prognostic and therapeutic target\cite{54}. As an oncogene for HCC, lncRNA HOTAIR inhibits the expression of miR-122 by mediating aberrant methylation of CpG islands in its promoter region, leading to the subsequent upregulation of cyclin G1 and HCC tumorigenesis\cite{55}. Hypomethylation of lncRNA34a promoter region resulted in its upregulation in HCC, which affected the bone metastasis of HCC by activating TGF-β signal pathway\cite{56}. Thus, targeting lncRNA34a is a potential treatment approach for HCC\cite{56}. In addition, lncRNA research results complement the mechanisms related to the development and metastasis of HCC and provide new research directions for the diagnosis, prognosis, and treatment of tumors in the future.

5 Summary and prospect

The continuous development of emerging technologies such as high-throughput sequencing in recent years is accompanied by numerous studies on various types of RNA methylation modification and a growing understanding of the related regulatory effects of RNA methylation modification on different cancers. A line of evidence points out that RNA methylation affects gene transcription through abnormal expression of various key enzymes, which playing distinct roles in HCC pathogenesis. It is noteworthy that in HCC, the abnormal expression of various key enzymes involved in the modification of mRNA m^6^A affects the progression of HCC, and the selection of one or several key enzymes as major biomarkers may help HCC diagnosis. Therefore, more studies are needed to expand the RNA modification bioinformatics network so as to identify representative markers for early diagnosis, prognosis, or targeted therapy of HCC.

The HCC is known for its high mortality rate, mainly due to high recurrence and metastasis. Given the importance of RNA methylases and demethylases in the regulation of HCC development, it is of great interest to develop effective and targeted inhibitors against the key enzymes that are responsible for the reversible RNA methylation modification in order to halt the HCC progression. Methylation-related regulators are usually regulated by downstream transcription factors. Therefore, in addition to treatment methods that directly target various key enzymes, therapy targeting downstream
regulatory proteins should also be considered as a potentially useful treatment approach. As an emerging field, the study of RNA methylation in cancer not only reveals the regulatory role of epigenetic changes in HCC but also provides new insights into its pathogenesis, early diagnosis, targeted therapy, and prognosis. Hence, a deeper understanding of m\textsuperscript{6}A modification would greatly improve the clinical aspects of HCC in the near future.

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**Conflicts of interest**

None of the authors has any potential conflicts to disclose.

**Authors’ contributions**

H.D. and B.T. conceived the idea of this review. H.D. and L.D. wrote the paper. H.S., G.S., S.L., and Z.W. revised the paper.

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