Epigenetic Regulation of m⁶A Modifications in Human Cancer

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N6-methyladenosine (m⁶A) is the most prevalent internal RNA modification, especially within eukaryotic messenger RNAs (mRNAs). m⁶A modifications of RNA regulate splicing, translocation, stability, and translation into proteins. m⁶A modifications are catalyzed by RNA methyltransferases, such as METTL3, METTL14, and WTAP (writers); the modifications are removed by the demethylases fat mass and obesity-associated protein (FTO) and ALKBH5 (ALKB homolog 5) (erasers); and the modifications are recognized by m⁶A-binding proteins, such as YTHDF domain-containing proteins and IGF2BP3 (readers). Abnormal changes in the m⁶A levels of these genes are closely related to tumor occurrence and development. In this paper, we review the role of m⁶A in human cancer and summarize its prospective applications in cancer.

N6-methyladenosine is an epigenetic modification of RNA molecules that was discovered in the early 1970s in messenger RNAs (mRNAs) from eukaryotes.¹ Due to the limitations of detection technology, scientists initially thought that m⁶A modification sites existed only in mRNA, but recent studies have found that m⁶A modifications exist in various types of RNA,² such as rRNAs, small nuclear RNAs (snRNAs), and microRNAs. With the rapid development of high-throughput sequencing technology and the gradual progress of epigenetic research, the functions of m⁶A modification in different biological processes have attracted people’s attention again. At present, there are mature single-site or even high-throughput single-site detection methods that can accurately and effectively detect m⁶A sites.

DNA carries the genetic information that is transcribed to generate mRNAs, which are then translated to generate functional proteins. In the process of cancer transformation, m⁶A modification can influence the development of tumors by regulating the mRNA expression level of oncogenes and suppressor genes. Similar to DNA methylation, m⁶A modification is regulated by methyltransferase and demethylase, and regulates the posttranscriptional expression level of genes without changing the base sequence, but the regulatory mechanism of m⁶A is complex. Emerging evidence suggests that m⁶A is involved in various aspects of RNA metabolism, including pre-mRNA splicing, 3’ end processing, nuclear export, translation regulation, mRNA decay, and noncoding RNA (ncRNA) processing.³ Furthermore, we summarize the association between m⁶A and human cancer occurrence and development to discover new markers and potential targets for molecular pathological diagnosis and molecular targeted therapy. The present review introduces m⁶A and describes the detection methods of m⁶A modification and its relationship with human cancer.

m⁶A Modification of RNA

Molecular Mechanism of m⁶A Modification
m⁶A modification mainly occurs at the consensus motif of RRM⁶ACH ([A/G/U][A/G]m⁶AC[A/C/U]), and the modification is enriched in 3’ untranslated regions (3’ UTRs), near stop codons and within internal long exons.⁴ The first type of protein involved in m⁶A regulation is the m⁶A methyltransferase, which possesses the ability to modify RNA with m⁶A modification; coding genes for these enzymes are called writing genes (writers). m⁶A modification is catalyzed by a multicomponent methyltransferase complex.⁵ METTL3, METTL14, and WTAP were the earliest writers discovered, and the complexes they form jointly promote the incorporation of the m⁶A methylated group into RNA.⁶–⁸ A newly discovered methyltransferase, METTL16, the paralog of METTL3, controls cellular SAM levels and methylates U6 snRNA.⁹ Subsequently, more new proteins, such as KIAA1429, RBM15³–¹² (and its paralog RBM15B¹²), and ZC3H13,¹³,¹⁴ have been identified as components of the methyltransferase complex and as essential for m⁶A modification.

The second type of protein is the m⁶A demethylase, which can remove m⁶A methylated groups from RNA; its coding genes are known eraser genes (erasers), indicating that m⁶A modification is actually a dynamic reversible process Figure 1. The common erasers include FTO¹⁵ and ALKBH5 (ALKB homolog 5).¹⁶ In addition, another
m^6A demethylase, ALKBH3 (ALKB homolog 3), has been found in recent studies.17 Interestingly, ALKBH3 preferentially acts on m^6A in tRNA rather than in mRNA or rRNA. Because there are other members of the ALKB subfamily with unknown functions,18 the discovery of more m^6A demethylases is unsurprising.

The last type of m^6A regulatory protein can bind to the m^6A modification site in RNA and play a specific role. The coding genes for these proteins are called readers. For the m^6A group to have a biological function, it needs to be identified by variable "readers," which initiate different downstream effects.19 The earliest readers were coding genes in the YTH domain family proteins, including YTHDF and YTHDC subtypes, such as YTHDC1, YTHDC2, YTHDF1, YTHDF2, and YTHDF3.20 Later, several readers were found: eIF3, HNRNP C, and HNRNP A2/B1.21 Interestingly, ALKBH3 preferentially acts on m^6A in tRNA rather than in mRNA or rRNA. Because there are other members of the ALKB subfamily with unknown functions,18 the discovery of more m^6A demethylases is unsurprising.

Figure 1. A Schematic Diagram Illustrates the Molecular Mechanisms and Functions of m^6A Methylation

Complexes formed by METTL3, METTL14, WTAP, RBM15, and METTL16 are named writers. ALKBH5 and FTO are common erasers. YTHDC1, YTHDF1, and YTHDF3 are common readers. Different readers binding to m^6A sites can produce different biological effects.

It is expected that in the future, there will be a more comprehensive understanding of the biological function of m^6A modification so that epigenetics can generate more knowledge regarding the regulation of gene expression at the posttranscriptional level.

Methods of m^6A Modification Detection

The identification of m^6A sites was initially very difficult, because m^6A modification of RNA does not affect its reverse transcription. However, with the emergence of second-generation sequencing, two similar m^6A modification site detection technologies were created: m^6A sequencing (m^6A-seq)34 and combine m^6A-specific methylated RNA immunoprecipitation with next-generation sequencing (MeRIP-seq).35 In the two detection methods, m^6A methylated RNA fragments are captured by immunoprecipitation.
technology and then identified by second-generation sequencing. These two methods revealed m^6^A to be a pervasive and dynamically reversible modification, particularly enriched in 3’ UTRs and near mRNA stop codons. The shortcoming of this method is that the RNA fragments captured by this technique are limited to approximately 100–200 nt, and the technique cannot identify two m^6^A sites that are very close to each other; therefore, this method cannot accurately identify m^6^A modification sites in the whole transcriptome. Another technique for detecting m^6^A modification level is m^6^A-level and isoform-characterization sequencing (m^6^A-LAIC-seq), which is similar to m^6^A-seq but introduces spiked-in RNAs as an internal reference; the spiked-in RNAs are used to calculate the m^6^A modification level of each gene in the whole transcriptional group, but single m^6^A modification sites cannot be detected.

Other methods have been developed to improve resolution, such as PA-m^6^A-Seq (photo-crosslinking-assisted m^6^A sequencing), m^6^A individual-nucleotide-resolution cross-linking and immunoprecipitation (miCLIP), and m^6^A-CLIP. In these methods, UV strengths the crosslink between m^6^A-containing RNA fragments and m^6^A antibodies, and then antibody-RNA complexes are obtained through affinity purification. m^6^A modification sites can be more accurately detected at a single-base resolution of RNA using site-specific cleavage and radioactive-labeling followed by ligation-assisted extraction and thin-layer chromatography (SCARLET) immunoprecipitation techniques.

In 2013, SCARLET was developed. This method can accurately detect a single m^6^A modification site in mRNAs and lncRNAs, and can calculate the m^6^A modification level of the whole RNA. Although SCARLET is incapable of high-throughput screening and is time-consuming, it is relatively expensive, and its high accuracy makes it a common method used to check the accuracy of high-throughput detection of m^6^A methylated sites.

Recently, Garcia-Campos et al. developed MAZTER-seq, which allows systematic m^6^A quantitation by digesting RNA via antibody-independent methods; the results revealed that antibody-based methods are of limited sensitivity. This method can quantitatively track m^6^A in diverse biological settings, but it also has limitations. Only when a subset of RNA sites occurs at ACA sites and is within suitable distances of adjacent ACA sites can m^6^A be quantified.

Furthermore, Liu et al. reported RNAmod, which provides intuitive interfaces to show outputs, including the distribution of RNA modifications, modification coverage for different gene features, functional annotation of modified mRNAs, and comparisons between different groups or specific gene sets.

However, our current knowledge about dynamic changes in m^6^A levels and how the change in m^6^A levels for a specific gene can play a role in certain biological processes is largely elusive. To address this lack of knowledge, Zhang et al. proposed FunDMDDeep-m^6^A, which is a novel pipeline for identifying context-specific (e.g., disease versus normal, differentiated cells versus stem cells, or gene knockdown cells versus wild-type cells) m^6^A-modified functional genes.

Liu et al. showed that, using direct RNA sequencing, m^6^A RNA modifications could be detected with high accuracy in the form of systematic errors and decreased base-calling qualities. Specifically, they found that an algorithm, trained with m^6^A-modified and unmodified synthetic sequences, could predict m^6^A RNA modifications with ~90% accuracy.

Zhang et al. developed a precise and high-throughput antibody-independent m^6^A identification method based on an m^6^A-sensitive RNA endoribonuclease that recognizes ACA motifs (m^6^A-sensitive RNA endoribonuclease-facilitated sequencing [m^6^A-REF-seq]). Whole-transcriptomic, single-base m^6^A maps generated by m^6^A-REF-seq quantitatively displayed an explicit distribution pattern with enrichment near stop codons. They used independent methods to validate the methylation status and abundance of individual m^6^A sites, confirming the high reliability and accuracy of the m^6^A-REF-seq data.

Although multiple methods have been developed to detect m^6^A modification, many difficulties and challenges remain at both single-base and quantitative sequencing levels, and more methods are desperately needed.

**Prediction of m^6^A Modification Sites**

Bioinformatics can greatly improve research efficiency by effectively predicting m^6^A modification sites (Table 1). Zhang et al. first proposed HMM (hidden Markov model) to predict residual sites around known sites. Subsequently, Liu et al. developed a faster and more stable method, pRNAm-PC, to predict sites. Moreover, Chen et al. developed the iRNA-Methyl method. The common feature of pRNAm-PC and iRNA-Methyl is the application of an SVM (support vector machine) model. On this basis, Jia et al. developed a RNA-methylPred method, which is more stable and efficient than the previous two. Subsequently, Li et al. proposed an improved TargetM^6^A method, but this method could predict only the methylation site of m^6^A in primary RNA sequences. Zhou et al. proposed the SRAMP method, which could more effectively predict m^6^A modification sites in mammalian RNA by integrating various mathematical models. Recently, a database website named rmbase-v2.0 was established, and it contains the sequencing data of multiple kinds of RNA epigenetic modifications in 13 species. This database contains a substantial amount of data on m^6^A modification sites, which can predict m^6^A modification information of RNAs to be studied.

Song et al. proposed a computational approach for the prediction of the target sites of m^6^A enzymes. Their method achieved reasonable performance on both writer target prediction (as high as 0.918) and eraser target prediction (as high as 0.888) in a 5-fold cross-validation analysis, and the results of the gene ontology analysis of their
m6A-binding YTH domain. APOBEC1-YTH expression in cells inhibits. In DART-seq, the cytidine deaminase APOBEC1 is fused to the and the Flt3 gene were most significantly affected.55 The downregulation of METTL3 gene expression promotes the differentiation of hematopoietic stem cells into AML cells, suggesting that METTL3 may be a potential therapeutic target for KMT2A-MLLT3 and mutated Flt3 in AML. Vu et al.56 also reported that METTL3 was associated with the occurrence and development of AML. This study found that the pAKT gene expression in CD34+ hematopoietic stem cells increased after the METTL3 gene was downregulated, thus promoting the differentiation of normal hematopoietic stem cells into AML cells and vice versa. It was also found that m6A modification promoted the transcription of c-MYC, BCL2, and PTEN in CD34+ hematopoietic stem cells.57 Recently, Han et al.58 found that METTL3 may positively regulate the pri-miR221/222 process in a m6A-dependent manner by interacting with the microprocessor protein DGCR8, thereby exerting a carcinogenic effect in bladder cancer. In addition, Jin et al.59 demonstrated an oncogenic role of m6A-modified IGFL6, showing its regulatory mechanisms in bladder cancer development and progression, thus identifying a potential therapeutic target for bladder cancer. Yang et al.60 confirmed the dynamic modification of m6A in chemically induced malignant transformation and provided insight into the key role of the METTL3-m6A-CDCP1 axis in chemical carcinogenesis. In addition, Cheng M et al.61 recently found that the AFF4/NF-KB/MYC signaling network is modulated by METTL3-mediated m6A and provided insight into the mechanism of bladder cancer progression. Recently, Li et al.62 found that m6A modulates nonsense-mediated mRNA decay in human glioblastoma, revealing a novel function for m6A in modulating NMD and uncovering the mechanism by which METTL3 promotes glioblastoma multiforme (GBM) tumor growth and progression. Li et al.63 revealed that METTL3, acting as an oncogene, maintained SOX2 expression through an m6A-IGF2BP2-dependent mechanism in CRC (colorectal carcinoma) cells, and they suggested a panel of potential biomarkers for prognostic prediction of CRC.

Weng et al.64 found that the METTL14 gene in normal hematopoietic stem cells and mixed surface AML cells accompanied by (t(11q23) t(15;17)) or t (8;21) was highly expressed in normal differentiated bone marrow cells but poorly expressed in normal differentiated bone marrow cells. The METTL14 gene encodes a protein that increases m6A modification levels in some transcriptomes. In this study, it was found that knocking down the expression of METTL14 in AML cell lines reduced the stability of mRNA transcribed by MYB and MYC, and accelerated the degradation of the RNA. This indicates that MYB and MYC are regulated by METTL14. METTL14 plays a role in the differentiation of hematopoietic stem cells into AML cells and plays a role in the development and maintenance of leukemia and self-renewal. Silent expression of METTL14 can effectively inhibit the proliferation of AML cell lines. The effect of the SPY1-METTL14-MYB/MYC pathway on AML was revealed, providing a new direction for the diagnosis and treatment of AML. Chen et al.65 found that METTL3 can change the m6A modification level of the tumor suppressor gene SOCS2. In addition, METTL3 overexpression can promote the proliferation and migration of hepatocellular carcinoma.

| Table 1. Methods for Detection and Prediction of m6A Methylation |
|------------------|------------------|
| Methods          | Features         |
| Detection         |                  |
| m6A-Seq54         | high throughput  |
| MeRIP-seq58       | high throughput  |
| m6A-LAIC-seq60    | high throughput, precise |
| PA m6A-Seq77      | high throughput, single site |
| m6CLIP61          | high throughput, single site |
| m6A-CLIP62        | high throughput, single site |
| SCARLET63         | high throughput, single site |
| MAXZTER-seq51     | high throughput, single site |
| RNAmod52          | high throughput, single site |
| FunDMD-m6A53      | high throughput, single site |
| DART-seq         | high throughput, single site |
| RNA sequencing41  | high throughput, single site |
| m6A-REF-seq44     | high throughput, single site |
| Prediction        |                  |
| HMM47            | database         |
| pRNAm-PC37        | database         |
| iRNA-Methyl48     | database         |
| RNA-methylPred47  | database         |
| TargetmA66        | database         |
| SRAMP41           | database         |
| RMbase-v2.052     | database         |
| DART-seq92        | database         |

preferential targets further revealed the functional relevance of different RNA methylation writers and erasers.

Meyer44 presented DART-seq (deamination adjacent to RNA modification targets), which is an antibody-free method for detecting m6A sites. In DART-seq, the cytidine deaminase APOBEC1 is fused to the m6A-binding YTH domain. APOBEC1-YTH expression in cells induces C-to-U deamination at sites adjacent to m6A residues, which are detected using standard RNA-seq.

m6A Modification and Tumors

m6A Hypermethylation and Tumors

m6A modification is involved in the differentiation process of hematopoietic stem cells in vertebrates, suggesting that m6A modification may be closely related to the occurrence and development of hematopoietic tumors in the blood system. The METTL3 gene has different effects on the proliferation and growth of mouse and human acute myeloid leukemia cell lines; among them, Acute myeloid leukemia (AML) cell lines expressing the KMT2A-MLLT3 fusion gene and the Flt3 gene were most significantly affected.55 The downregulation of METTL3 gene expression promotes the differentiation of AML cells. Due to the regulation of METTL3 expression by the transcription factor CEBPZ, the m6A modification levels of mRNA transcribed by the oncogene SP1 increase significantly when METTL3 is downregulated, eventually leading to an increase of SP1 protein expression. SP1 protein can continuously affect the differentiation of hematopoietic stem cells into AML cells, suggesting that METTL3 may be a potential therapeutic target for KMT2A-MLLT3 and mutated Flt3 in AML. Vu et al.56 also reported that METTL3 was associated with the occurrence and development of AML. This study found that the pAKT gene expression in CD34+ hematopoietic stem cells increased after the METTL3 gene was downregulated, thus promoting the differentiation of normal hematopoietic stem cells into AML cells and vice versa. It was also found that m6A modification promoted the transcription of c-MYC, BCL2, and PTEN in CD34+ hematopoietic stem cells.57 Recently, Han et al.58 found that METTL3 may positively regulate the pri-miR221/222 process in a m6A-dependent manner by interacting with the microprocessor protein DGCR8, thereby exerting a carcinogenic effect in bladder cancer. In addition, Jin et al.59 demonstrated an oncogenic role of m6A-modified IGFL6, showing its regulatory mechanisms in bladder cancer development and progression, thus identifying a potential therapeutic target for bladder cancer. Yang et al.60 confirmed the dynamic modification of m6A in chemically induced malignant transformation and provided insight into the key role of the METTL3-m6A-CDCP1 axis in chemical carcinogenesis. In addition, Cheng M et al.61 recently found that the AFF4/NF-KB/MYC signaling network is modulated by METTL3-mediated m6A and provided insight into the mechanism of bladder cancer progression. Recently, Li et al.62 found that m6A modulates nonsense-mediated mRNA decay in human glioblastoma, revealing a novel function for m6A in modulating NMD and uncovering the mechanism by which METTL3 promotes glioblastoma multiforme (GBM) tumor growth and progression. Li et al.63 revealed that METTL3, acting as an oncogene, maintained SOX2 expression through an m6A-IGF2BP2-dependent mechanism in CRC (colorectal carcinoma) cells, and they suggested a panel of potential biomarkers for prognostic prediction of CRC.

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WTAP as a potential therapeutic target for HCC treatment. 

Radiation and chemotherapy, which may be because of their expression of both FTO and β-catenin alone. Therefore, the expression of FTO and β-catenin has a certain prognostic value for evaluating the clinical progression of CSCC. METTL3 and METTL14 were significantly reduced in CSCC, whereas FTO and ALKBH5 were significantly increased. It is speculated that m6A hypomethylation may play an important role in the occurrence and development of cervical cancer. Disease-free survival (DFS) and overall survival (OS) of m6A hypomethylated patients were significantly reduced, and hypomethylated patients had a higher recurrence rate (p < 0.01). Hypermethylation of m6A in cervical cancer cells can significantly inhibit proliferation. Yang et al. demonstrated a crucial role of FTO as an m6A demethylase in promoting melanoma tumorigenesis and anti-PD-1 (PDCD-1) resistance, and the authors suggested that the combination of FTO inhibition with anti-PD-1 treatment may reduce the resistance to immunotherapy in melanoma. Niu et al. showed that FTO, a key m6A demethylase, was upregulated in human breast cancer. A high level of FTO was significantly associated with lower survival rates in patients with breast cancer. Because the methylation level of m6A in tumors often depends on the levels of transmethylase and demethylase, the study of the gene expression levels of these two enzymes in tumors adds to the in-depth understanding of the correlation between the occurrence and development of tumors and m6A modification, which could help establish a new method for early diagnosis and prognostic analysis of tumors Table 2.

Table 2. m6A Methylation-Related Tumor

| Related Proteins that Encode Genes | Trend | Cancer | Regulatory Gene |
|-----------------------------------|-------|--------|-----------------|
| Writers                           |       |        |                 |
| UP | leukemia | SP1, c-MYC, BCL2, PTEN |
| UP | hepatoma | SOCS2 |
| METTL3 |       |        |                 |
| UP | bladder cancer | DGC88, CDCP1, AFF4/NF-κB/MYC |
| DOWN | glioblastoma | ADAM19, EPHA3, KL4, CDKN2A, BRCA2, TP53 |
| UP | colorectal carcinoma | IGF2BP2 |
| METTL14 |       |        |                 |
| DOWN | glioblastoma | ADAM19, EPHA3, KL4, CDKN2A, BRCA2, TP53 |
| WTAP |       |        |                 |
| UP | hepatoma | ET5 proto-oncogene 1 |
| Erasers                           |       |        |                 |
| UP | leukemia | ASB2, RARA, TP53 |
| FTO | UP | cervical carcinoma | β-catenin pathway |
| | UP | melanoma | autophagy and NF-κB pathway, BNIP3 |
| ALKBH5 |       |        |                 |
| UP | breast carcinoma | KL4, NANO |
| Readers                           |       |        |                 |
| UP | colorectal cancer | |
| UP | hepatoma | |
| YTHDF1 |       |        |                 |
| UP | colorectal cancer | |
| UP | hepatoma | |
| YTHDF2 |       |        |                 |
| UP | hepatoma | SOCS2 |

m6A Hypomethylation and Tumors

The concentrated expression of FTO at the mixed lineage leukemia (MLL) gene site in reprogrammed AML cells could reduce the methylation level of m6A in the mRNA of ASB2 and RARA genes, thus leading to the occurrence and development of AML. Recently, Paris et al. demonstrated that YTHDF2 is also a key factor for cancer stem cells in AML. They found that inhibition of YTHDF2 specifically compromises leukemic stem cell (LSC) development and propagation. At the same time, they found that the high expression of FTO could inhibit the differentiation of AML cells into normal blood cells following treatment with all-trans-retinoic acid. This makes FTO, which is a demethylase, an oncogene related to MLL in AML. In cervical squamous cell carcinoma (CSCC), FTO expression was significantly increased, and it was found that these patients developed tolerance to radiotherapy and chemotherapy, which may be because of FTO reducing the m6A modification level of some genes, thereby activating the β-catenin pathway and affecting the expression of ERCC1. Increased expression of both FTO and β-catenin in patients with CSCC presented a worse prognosis than for patients with increased expression of both FTO and β-catenin alone. Therefore, the expression of FTO and β-catenin has a certain prognostic value for evaluating the clinical progression of CSCC. METTL3 and METTL14 were significantly reduced in CSCC, whereas FTO and ALKBH5 were significantly increased. It is speculated that m6A hypomethylation may play an important role in the occurrence and development of cervical cancer. Disease-free survival (DFS) and overall survival (OS) of m6A hypomethylated patients were significantly reduced, and hypomethylated patients had a higher recurrence rate (p < 0.01). Hypermethylation of m6A in cervical cancer cells can significantly inhibit proliferation. Yang et al. demonstrated a crucial role of FTO as an m6A demethylase in promoting melanoma tumorigenesis and anti-PD-1 (PDCD-1) resistance, and the authors suggested that the combination of FTO inhibition with anti-PD-1 treatment may reduce the resistance to immunotherapy in melanoma. Niu et al. showed that FTO, a key m6A demethylase, was upregulated in human breast cancer. A high level of FTO was significantly associated with lower survival rates in patients with breast cancer. Because the methylation level of m6A in tumors often depends on the levels of transmethylase and demethylase, the study of the gene expression levels of these two enzymes in tumors adds to the in-depth understanding of the correlation between the occurrence and development of tumors and m6A modification, which could help establish a new method for early diagnosis and prognostic analysis of tumors Table 2.

m6A Modification Readers and Tumors

Reading proteins can specifically bind to m6A sites in RNA, and different reading proteins will produce different biological functions after binding to m6A sites. For example, the YTHDF2 protein binds to the m6A site in the mRNA to accelerate the degradation of mRNA. When the m6A modification level of mRNA for the tumor suppressor gene SOCS2 in HCCs is upregulated, the YTHDF2 protein has more m6A binding sites and ultimately promotes mRNA degradation. The YTHDF1 gene is highly expressed in patients with colorectal cancer. Stratification of clinicopathological data showed that the expression of the YTHDF1 gene was correlated with tumor diameter, lymph node metastasis, distant metastasis, and clinical stage, but the specific regulatory mechanisms were not studied. Yang et al. collected samples from 31 HCC patients with stage III TNM and found that the increased expression rate of YTHDF2 was as high as 83.9% (26/31), suggesting that HCC patients at an advanced stage were most likely to have YTHDF2 protein binding to the m6A site of some genes. Subsequently, the author overexpressed miR-145 in HepG2 cell lines to reduce the expression of YTHDF2, and found that the proliferation of HepG2 cells was significantly inhibited, suggesting that miR-145 may be used as a potential therapy for HCC. Zhao et al. studied the liver cancer data in The Cancer Genome Atlas (TCGA) and found that the expression of YTHDF1 was significantly upregulated in patients with stage III and IV TNM compared with patients with stage II HCC, and the
patients with high levels of YTHDF1 had a worse prognosis. It was found that the potential target genes regulated by YTHDF1 protein may be related to the degradation of various amino acids and lipid metabolism of tumor cell cycles, and the abnormal physiological functions of these cells may be related to the occurrence and development of HCC. Finally, the author verified that c-Myc is the upstream gene regulating YTHDF1 through analysis of the TCGA and chromatin immunoprecipitation (ChIP)-atlas database prediction data and experiments.

Conclusions

m6A modification is one of many types of RNA epigenetic modification. Based on the current understanding of its association with tumors, m6A modification is not good or bad in itself, and it mainly promotes or inhibits the production of tumor cells by regulating the mRNA levels of related oncogenes or suppressor genes. Li et al.76 analyzed the foundational landscape of molecular alterations and clinically relevant m6A regulators; they also provided insights into the development of related therapeutic targets. With increasing research on the m6A modification mechanism, it was found that m6A modification enables more complex and diverse regulation of related RNA levels. Interestingly, simply the binding of a protein to the m6A modification site may not only promote the expression of related mRNAs but also reduce the stability of related mRNAs and accelerate degradation. In addition, ncRNAs can regulate the expression level of target genes, and when m6A modification occurs in ncRNA, the expression level of the ncRNA itself is regulated. The two-sided regulation of m6A modification, especially the regulation of ncRNA, might provide a new perspective to clarify some problems that could not be originally explained.29 The m6A modification level in RNA is closely related to the expression level of writing and erasing genes in cells, whereas the proteins that are readers bind to the m6A modification site to initiate a series of biological functions. Therefore, in tumors, changes in the expression level of both m6A-related genes and proteins are likely to be potential markers for tumor molecular diagnosis and may provide new targets for the research and development of clinical molecular targeted therapies.

Author Contributions

W.Z., X.Q., and L.L. wrote and drafted the manuscript and figures. J.W., J.I., and Z.L. revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no competing interests.

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