Recent advances in crosstalk between N6-methyladenosine (m6A) modification and circular RNAs in cancer

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N6-methyladenosine (m6A), as the most common RNA modification, plays a vital role in the development of cancers. Circular RNAs (circRNAs) are a class of single-stranded covalently closed RNA molecules. Recently, m6A modification has been identified as performing biological functions for regulating circRNAs. Increasing evidence also shows that circRNAs are involved in cancer progression by targeting m6A regulators. In this review, we describe the functional crosstalk between m6A and circRNAs, and illustrate their roles in cancer development. m6A methylation mediates the biogenesis, stability, and cytoplasmic export of circRNAs in different cancer types. Moreover, circRNAs regulate the expression of m6A regulators, participate in the degradation of m6A regulators, and regulate the m6A modification of target mRNAs. Finally, we discuss the potential applications and future research directions of m6A modification and circRNAs in cancer. Further understanding of the biological roles of m6A and circRNAs will provide new insight into the diagnosis and treatment of cancer patients.

BACKGROUND

According to recent global statistics, cancer is still an important factor that influences human health.1 N6-methyladenosine (m6A), as the most common RNA modification, has attracted increasing attention in the field of cancer development.2,3 m6A regulators might result in abnormal m6A levels in cancer cells to regulate oncogenes and tumor suppressor genes, which contribute to the development and prognosis of cancer patients.4–7

Circular RNAs (circRNAs) were first reported as single-stranded covalently closed RNA molecules in 19768 that were generated via the process of back-splicing.7 Emerging studies have revealed that circRNAs play vital roles in the occurrence and development of different diseases such as cancers.8–17 It has been revealed that the biological functions of circRNAs include acting as transcriptional regulators, microRNA sponges,14,15 protein templates, decoys, scaffolds, and recruiters16,17; however, studies on how circRNAs are regulated before exerting specific biological functions are still limited.18

m6A modification has been discovered in various noncoding RNAs (ncRNAs) including microRNAs, long ncRNAs (lncRNAs), circular RNAs (circRNAs),19 ribosomal RNAs (rRNAs), and small nuclear RNAs (snRNAs). m6A modification has been found to be essential for the metabolism and functions of ncRNAs. For example, Zhang et al. summarized the role of m6A modification in the regulation and function of circRNAs, in which m6A modification regulates circRNA translation and degradation and modifies circRNA in innate immunity.19 More interestingly, ncRNAs also participate in the regulation of m6A modification, thereby regulating their target mRNAs. Previous studies have investigated the crosstalk between m6A modification and ncRNAs in the development and treatment of cancer.20–22 However, the roles of m6A and circRNAs in cancer have not been reviewed comprehensively.

In this review, we describe the functional crosstalk between m6A and circRNAs in cancers. m6A methylation mediates the biogenesis, stability, and cytoplasmic export of circRNAs in different cancer types. Moreover, circRNAs regulate the expression of m6A regulators, participate in the degradation of m6A regulators, and regulate the m6A modification of target mRNAs. Finally, we investigate the biological roles of m6A and circRNAs in cancer development, which promote the clinical application of m6A and circRNAs for cancer patients.

MOLECULAR COMPOSITIONS OF m6A METHYLATION

m6A modification is regulated by m6A regulators including methyltransferases (writers), demethylases (erasers), and m6A-binding proteins.16,23,24 How-ever, the roles of m6A and circRNAs in cancer have not been reviewed comprehensively.
Regardings the biological functions of circRNAs, the most classical network is that circRNAs act as competing endogenous RNAs (ceRNAs). With miRNA response elements, circRNAs can function as "miRNA sponges" to bind specific miRNAs to negatively regulate their activity. Furthermore, circRNAs can also exert protein binding abilities by interacting with some RBPs to inhibit their function or transport. Recent studies have shown the abnormal expression of circRNAs in various cancers. The expression and function of circRNAs in cancer might be partly attributed to their epigenetic modification, and m6A modification is the first notable role (Figure 1).

CHARACTERISTICS AND BIOLOGICAL FUNCTIONS OF circRNAs

As a dynamic and reversible RNA modification, m6A can be regulated by m6A writers and erasers, which exhibit the complexity of epigenetic modifications. Two demethylases, alkB homolog 5 (ALKBH5) and fat mass and obesity-associated protein (FTO), have been identified as m6A erasers. Moreover, m6A modifications in an RNA structure might be selectively recognized by some RNA-binding proteins (RBPs), named m6A readers. The m6A readers mainly consist of the YT521-B homology (YTH) domain-containing protein family (YTHDC1-2, YTHDF1-3), the heterogeneous nuclear ribonucleoprotein (HNRNP) family (HNRNPA2B1, HNRNPC, and HNRNPG), and IGF2BPs. However, a new understanding of these proteins has led to the reversal of early concepts regarding the reading, writing, and erasing of m6A. In this review, we summarize recent advances in research on m6A and circRNAs, and we highlight how these new findings have reshaped our understanding of how m6A is regulated by circRNAs in cancer.

m6A MODIFICATION OF circRNAs IN CANCER

m6A methylation mediates the biogenesis of circRNAs

METTL3 is the key component of the methyltransferase complex and plays a vital role in cancers. A study by Li et al. investigated the biological function of circRNAs derived from METTL3 in breast cancer. In their study, METTL3, as the host gene of circMETTL3, was found to regulate circMETTL3 expression in an m6A-dependent manner. They further downregulated METTL14 or FTO to modify the m6A level of circMETTL3. Downregulated METTL14 reduced circ-METTL3 expression and increased pre-METTL3 expression, while decreased FTO expression caused the opposite effect. Their study provided novel insight into the relationship between circRNAs and the corresponding host genes. Chen et al. found that METTL3 induced circ1662 expression by binding its flanking sequences and installing m6A modification in colorectal cancer (CRC).

Researchers have reported that the alternative splicing of RNA can be regulated by m6A modification. Moreover, circRNAs are derived from their parental pre-mRNAs by alternative splicing. KIAA1429 is an important part of the m6A methyltransferase complex. Liu et al. aimed to identify KIAA1429-regulated circRNAs in hepatocellular carcinoma (HCC) via RNA sequencing and methylated RNA immunoprecipitation sequencing (MeRIP-seq). They found that the regulatory effect of KIAA1429 in the production of circDLC1 is involved in the processing of preDLC1. The detailed mechanism of KIAA1429-mediated alternative splicing during the processing of preDLC1 into circDLC1 requires further investigation. Rao et al. also reported that the m6A reader YTHDC1 bound to m6A-modified circ-ARL3 and favored its reverse splicing and biogenesis in the development of HBV + HCC.

m6A methylation maintains the stability of circRNAs

Wu et al. found that METTL3 mediated m6A methylation and stabilized the expression of circCUX1, which is involved in radiotherapy tolerance in hypopharyngeal squamous cell carcinoma (HPSCC) patients. In cervical cancer (CC), Chen et al. revealed that circ0000069 was upregulated partially due to m6A modification, which maintained the stability of circ0000069. Xu et al. found that the m6A level...
of circRNA-SORE was increased in sorafenib-resistant cells, and circRNA-SORE expression was downregulated when its m6A modification was inhibited. Accordingly, m6A regulates circRNA-SORE expression by increasing its stability; however, no remarkable differences in the expression levels of m6A-related proteins were found in sorafenib-resistant cells. The underlying mechanisms of increased circRNA-SORE m6A levels in sorafenib-resistant cells should be further illustrated.

**m6A methylation mediates the translation of circRNAs**

Internal ribosome entry sites (IRESs) are sequences that can activate a cap-independent translation process by binding ribosomes with RNAs including circRNAs. Recently, another cap-independent pathway driven by m6A was reported by Yang et al. In response to environmental stress, circRNAs containing m6A motifs are activated by eIF4G2 and YTHDF3. Moreover, methyltransferases (such as METTL3/14) can enhance the translation process, while demethylase FTO inhibits it. In particular, Legnini et al. indicated that the above pathways may have some connections since they found that the m6A methylation level was enhanced in some IRES-activated protein-coding circRNAs. These results reveal that m6A methylation mediates circRNA translation through delicate mechanisms. However, the role of m6A methylation in the translation of circRNAs has not been thoroughly investigated in cancer to date.

**m6A methylation mediates the degradation of circRNAs**

CircRNAs are more stable due to their single-stranded covalently closed structure. It has been reported that circRNAs are less likely to degrade than their corresponding parental linear RNAs. However, how circRNAs are degraded and what factors accelerate their degradation remain largely unknown. A previous study by Wang et al. revealed that m6A can regulate mRNA degradation via selective recognition by YTHDF2. They further developed a mechanistic model that indicated that C-YTHDF2 selectively binds to m6A-modified mRNAs. N-YTHDF2 commits to degradation by localizing the YTHDF2-m6A-mRNA complex to more specialized mRNA decay sites. On this basis, Du et al. further corrected the model and revealed the mechanism of m6A-containing RNA degradation mediated by YTHDF2. They demonstrated that N-YTHDF2 interacts directly with the SH domain of CNOT1 to recruit the CCR4-NOT complex, consequently accelerating the deadenylation of m6A-containing RNAs, which is important for the YTHDF2-mediated degradation of m6A-containing RNAs. Recently, it was reported that m6A-containing RNAs can be recognized and destabilized by the YTHDF2-HRSP12-RNase P/MRP axis. Park et al. showed that YTHDF2 can target m6A positions in linear and circular RNAs and mediate the endoribonucleolytic cleavage of m6A-modified RNAs by RNase. In addition, if there are HRSP12-binding sites

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**Table 1. m6A modification of circRNAs in cancer**

| m6A regulator | circRNA | Cancer type | Cell line type | Mechanism | Citation |
|---------------|---------|-------------|----------------|-----------|---------|
| METTL3        | circMETTL3 | Breast cancer | ZR-75-1, SUM1315 | METTL3 as the host gene of circMETTL3 may regulate circMETTL3 expression | Li et al. |
| METTL3        | circ1662 | CRC | HCT116, SW480 | METTL3 induced circ1662 expression by binding its flanking sequences and installing m6A modifications | Chen et al. |
| KIAA1429      | circDLC1 | HCC | Huh-7, SK-Hep1, SNU 449, HCC-LM9 | KIAAA1429-mediated alternative splicing during the processing of preDLC1 into circDLC1 | Liu et al. |
| YTHDC1        | circ-ARL3 | Hepatitis B virus-associated HCC | HepG2.2.15, HepG2 | YTHDC1 bound to m6A-modified of circ-ARL3 and favored its reverse splicing and biogenesis | Rao et al. |

**Stability of circRNAs**

| METTL3 | circCUX1 | HPSCC | SCC-9, Fadu cell lines | METTL3 mediated the m6A methylation and stabilized the expression of circCUX1 | Wu et al. |
| METTL3 | circ0000069 | CC | SiHa, Caski | circ0000069 was upregulated partially due to m6A modification, that maintained circ0000069 stability | Chen et al. |
| m6A | circRNA-SORE | HCC | HepG2, SKhep1, Huh7, LM3 | m6A modification regulates circRNA-SORE expression by increasing its stability | Xu et al. |

**Cytoplasmic export of circRNAs**

| YTHDC1 | circNSUN2 | CRC | HCT116, TC71 patient-derived xenograft cell line | m6A modification of circNSUN2 increases export to the cytoplasm | Chen et al. |

m6A, N6-methyladenosine; circRNAs, circular RNAs; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; HPSCC, hypopharyngeal squamous cell carcinoma; CC, cervical cancer.
near the m6A positions, the cleavage will be more thorough and specifically downregulate the target RNAs. These investigations indicate that m6A may mediate the downregulation of circRNAs; however, no relevant studies have been reported in cancer. Further in-depth experiments should be designed to explore whether m6A methylation mediates the degradation of circRNAs in cancer.

m6A methylation promotes the cytoplasmic export of circRNAs

CircRNAs might play a role at specific sites in cells. Chen et al. found that m6A of circNSUN2 increases cytoplasmic export in CRC. By functioning as the circNSUN2/IGF2BP2/HMGA2 complex in the cytoplasm, circNSUN2 could promote the stability of HMGA2 mRNA and the metastasis of CRC.

In summary, m6A modification of circRNAs in cancer mainly includes (1) mediating the biogenesis of circRNAs, (2) maintaining the stability of circRNAs, and (3) promoting the cytoplasmic export of circRNAs.

circRNAs REGULATE m6A MODIFICATION IN CANCER

circRNAs regulate the expression of m6A regulators via the ceRNA network

As elucidated by Ding et al., silencing circ_0072083 can downregulate NANOG expression by blocking ALKBH5-mediated demethylation. In detail, circ_0072083 regulates NANOG and ALKBH5 by sponging miR-1252-5p in glioma. Mo et al. revealed that hsa_circ_0072309 interacted with miR-607 via its miRNA response element to increase FTO expression, thus promoting tumorigenesis of non-small-cell lung cancer (NSCLC). Chi et al. validated that hsa_circ_0007456 (circMAP2K4) might facilitate HCC proliferation by sponging hsa-miR-139-5p to increase YTHDF1 expression.

circRNAs participate in the degradation of m6A regulators

Li et al. reported that circNDUF2B2 functions as a scaffold to enhance the interaction between TRIM25 and IGF2BPs. This TRIM25/circNDUF2B2/IGF2BP complex facilitates the ubiquitination and degradation of IGF2BPs, and this effect is enhanced by m6A modification of circNDUF2B2. In this way, circNDUF2B2 participates...
in the degradation of IGF2BPs and the activation of antitumor immunity during NSCLC progression.

**Table 2. circRNAs regulate m6A modification in cancer**

| circRNA              | m6A regulator | Cancer type | Cell line type | Mechanism                                                                 | Citation |
|----------------------|---------------|-------------|----------------|---------------------------------------------------------------------------|----------|
| circ_0072083         | ALKBH5        | Glioma      | U251, U87      | circ_0072083/miR-1252-5p/NANOG and ALKBH5                                  | Ding et al.63 |
| circ_0072309         | FTO           | NSCLC       | H1975, H1650   | circ_0072309/miR-607/FTO                                                  | Mo et al.64  |
| circMAP2K4/circ_0007456 | YTHDF1       | HCC         | MHCC97H, HCCLM3 | circMAP2K4/hsa-miR-139-5p/YTHDF1                                           | Chi et al.65 |
| cirncNDUFB2          | IGF2BPs       | NSCLC       | A549, H1299, H1650, H460 | TRIM25/cirncNDUFB2/IGF2BPs ternary complex facilitates ubiquitination and degradation of IGF2BPs | Li et al.66 |

m6A, N6-methyladenosine; circRNAs, circular RNAs; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; WTAP, Wilms’ tumor-associated protein; RBM15, RNA-binding motif protein 15; ALKBH5, alkB homolog 5; FTO, fat mass and obesity-associated protein; HCC, hepatocellular carcinoma; BC, bladder cancer; NSCLC, non-small-cell lung cancer; CSCs, cancer stem cells.

**THE REGULATIVE ROLES OF m6A MODIFICATION AND CIRCULAR RNAs IN CANCER**

**Tumor tumorigenesis**

METTL3 is the most important part of the methyltransferase complex, and can act as the host gene of circRNAs. In a study by Li et al.,67 circMETTL3, which is derived from METTL3, was found to act as a miR-31-5p sponge and upregulate cyclin-dependent kinases and promote cell proliferation, migration, and invasion in breast cancer. Chen et al.68 also confirmed that METTL3-induced circ1662 promoted CRC cell invasion and migration by accelerating YAP1 nuclear transport. Mechanistically, circ1662 directly bound to YAP1 and accelerated its nuclear accumulation to regulate the SMAD3 pathway. Moreover, circMEG3 can inhibit the growth of human liver CSCs in vivo and in vitro. circMEG3 inhibits the expression of Cbf5 through METTL3 dependent on HULC. As shown by Wang et al.,70 circ_KIAA1429 maintained the expression of Zeb1 through the mechanism of m6A-YTHDF3-Zeb1.

Regarding the function of m6A erasers and readers in tumorigenesis, Mo et al.64 declared that circ_0072309 sponges miR-607 to increase the expression of the m6A eraser FTO, thus promoting tumorigenesis of NSCLC. The m6A reader YTHDC1 bound to m6A-modified circ-ARL3 and favored its reverse splicing and biogenesis. Furthermore, circ-ARL3 can sponge miR-1305 to facilitate HBV + HCC progression.51 As shown by Wang et al.,70 circ_KIAA1429 induced the migration, invasion, and EMT of HCC and maintained the expression of Zeb1 via m6A-YTHDF3-Zeb1. IGF2BP1 was reported to bind with circPTPRA in the
cytoplasm of BC cells. Ectopic expression of circPTPRA abolished the promotion of the proliferation, migration, and invasion of BC cells induced by IGF2BP1.

Tumor metastasis
Liu et al.50 aimed to identify KIAA1429-regulated circRNAs in HCC via RNA sequencing and MeRIP-seq. CircDLC1 is a KIAA1429-regulated circRNA, and circDLC1 suppresses the growth and metastasis of HCC via the HuR-MMP1 axis. Chen et al.62 reported that upregulated circNSUN2 facilitates liver metastasis in PDX metastasis models in vivo and accelerates CRC cell invasion in vitro. By forming a circNSUN2/IGF2BP2/HMGA2 RNA-protein ternary complex in the cytoplasm, circNSUN2 promotes the stability of HMGA2 mRNA to facilitate CRC metastasis.

Tumor drug resistance and radiotherapy tolerance
Temozolomide (TMZ) resistance limits its clinical application in glioma. NANOG is an important biomarker for TMZ resistance. circ_0072083 can regulate NANOG and ALKBH5 by targeting miR-1252-5p to control TMZ resistance.63 Xu et al.54 revealed that circRNA-SORE sustains sorafenib resistance in HCC by acting as a miR-139-5p sponge to regulate the Wnt/β-catenin pathway. The m6A level of circRNA-SORE is increased in sorafenib-resistant cells, and m6A modification regulates circRNA-SORE expression by increasing its stability.

In HPSCC patients, Wu et al.52 found that circCUX1 is a potential therapeutic target for radiotherapy tolerance. METTL3 mediated the m6A methylation of circCUX1 and stabilized its expression. circCUX1 binds to Caspase1 and inhibits its expression, resulting in a decrease in the release of inflammatory factors, thereby developing tolerance to radiotherapy (Table 3).

CLINICAL APPLICATION AND FUTURE PROSPECTS
The functional crosstalk between m6A and circRNAs plays a vital role in the development of cancers, thus promoting their clinical application in cancer patients. First, m6A methylation and circRNAs could serve as new biomarkers for diagnosis and prognosis in cancer.71,72 High expression of YTHDF1 was correlated with high pathological grade, advanced stage, and poor survival of HCC. circMAP2K4 was validated to promote HCC cell proliferation by binding with miR-139-5p to promote YTHDF1 expression.65 Moreover, m6A methylation and circRNAs also participate in drug resistance and cancer treatment. As described above, m6A and circRNAs play a vital role in temozolomide63 and sorafenib64 resistance and the radiotherapy tolerance of cancers. Finally, m6A methylation and circRNAs...
Table 3. The regulative roles of m6A modification and circRNAs in cancer

| Function                         | m6A regulator | circRNA       | Cancer type | Mechanism                                      | Citation   |
|---------------------------------|---------------|---------------|-------------|-----------------------------------------------|------------|
| Tumor tumorigenesis             | METTL3        | circMETTL3    | Breast cancer | sponge miR-31-5p and upregulate cyclin-dependent kinases | Li et al.57 |
|                                 | METTL3        | circ1662      | CRC         | bound to YAF1 and accelerated its nuclear accumulation | Chen et al.58 |
|                                 | METTL3        | circMEG3      | Liver CSCs  | inhibit the expression of Che5                  | Jiang et al.59 |
|                                 | FTO           | circ_0072309  | NSCLC       | sponge miR-607 to increase the expression of FTO | Mo et al.64 |
|                                 | YTHDC1        | circ-ARL3     | Hepatitis B virus-associated HCC | sponge miR-1305 | Rao et al.51 |
|                                 | YTHDF3        | circ_KIAA1429 | HCC         | maintain the expression of Zeb1 via m6A-YTHDF3-Zeb1 | Wang et al.60 |
|                                 | IGF2BP1       | circPTPRA     | BC          | downregulate MYC and FSCN1 expression          | Xie et al.67 |
|                                 | KIAA1429      | circDLC1      | HCC         | via the HuR-MMP1 axis                          | Liu et al.68 |
| Tumor metastasis                | YTHDC1        | circNSUN2     | CRC         | form a circNSUN2/IGF2BP2/HMG2 RNA-protein ternary complex in the cytoplasm to promote the stability of HMG2 mRNA | Chen et al.69 |
|                                 | ALKBH5        | circ_0072083  | Glioma      | regulate NANO2 and ALKBH5 via targeting miR-1252-5p | Ding et al.65 |
| Tumor drug resistance and radiotherapy tolerance | m6A           | circRNA-SORE  | HCC         | sponge miR-103a-2-5p and miR-660-3p to regulate Wnt/b-catenin pathway | Xu et al.66 |
|                                 | METTL3        | circCUX1      | HPSCC       | bind to Caspase1 and inhibit its expression    | Wu et al.67 |

m6A, N6-methyladenosine; circRNAs, circular RNAs; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; ALKBH5, alkB homolog 5; FTO, fat mass and obesity-associated protein; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; HPSCC, hypopharyngeal squamous cell carcinoma; GC, cervical cancer; BC, bladder cancer; NSCLC, non-small-cell lung cancer; CSCs, cancer stem cells.

function in effective immunotherapy for cancer. circNDUFB2 participates in the degradation of IGF2BP3 and the activation of antitumor immunity during NSCLC progression via the modulation of both protein ubiquitination and degradation, as well as cellular immune responses. With the development of MeRIP-seq and miCLIP (m6A individual nucleotide-resolution cross-linking and immunoprecipitation) technologies, there is no doubt that they could greatly expand our understanding and drive more applications.

**CONCLUSIONS**

This review mainly discusses the functional crosstalk between m6A and circRNAs in cancers. m6A methylation mediates the biogenesis, stability, and cytoplasmic export of circRNAs in different cancer types. Moreover, circRNAs regulate the expression of m6A regulators, participate in the degradation of m6A regulators, and regulate the m6A modification of target mRNAs. Further understanding of the biological roles of m6A and circRNAs provides new insight into the diagnosis and treatment of cancer patients.

**AUTHOR CONTRIBUTIONS**

X.H., Z.W.S., and W.Y.Z. drafted the manuscript and prepared the figures. H.Y.G., I.T.W., and L.K.Y. collected the related references and participated in discussion. X.H., Z.W.S., and W.Y.Z. designed this review and revised the manuscript. All authors contributed to this manuscript. All authors read and approved the final manuscript.

**DECLARATION OF INTERESTS**

The authors declare that they have no competing interests.

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