



RNA N^6 -Methyladenosine in Cancer Metastasis: Roles, Mechanisms, and Applications

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Cancer metastasis is a symptom of adverse prognosis, a prime origin of therapy failure, and a lethal challenge for cancer patients. N^6 -methyladenosine (m^6A), the most prevailing modification in messenger RNAs (mRNAs) and non-coding RNAs (ncRNAs) of higher eukaryotes, has attracted increasing attention. Growing studies have verified the pivotal roles of m^6A methylation in controlling mRNAs and ncRNAs in diverse physiological processes. Remarkably, recent findings have showed that aberrant methylation of m^6A -related RNAs could influence cancer metastasis. In this review, we illuminate how m^6A modifiers act on mRNAs and ncRNAs and modulate metastasis in several cancers, and put forward the clinical application prospects of m^6A methylation.

Keywords: N^6 -methyladenosine methylation, cancer metastasis, non-coding RNAs, mRNAs, clinical applications

INTRODUCTION

The discovery of RNA methylation modification, as well as the exploration of its chemical structure and biological function, have opened up a new field of epigenetic research (1–4). As the most pervasive RNA modification, m^6A was extensively found in eukaryotes, prokaryotes and viruses (5–7). Foremost, the m^6A locus contains consensus motif “RRACH” and is associated with splicing factors, transcript abundance and mRNA half-life (8). Regulated by methyltransferases, demethylases and binding proteins, m^6A methylation is involved in the development of the skeletal system (9), nervous system (10), immune homeostasis (11), and pathological disease processes (12). Gene expression and biological functions various from the methylation levels of corresponding RNAs in distinct tissues, cell lines and research models (2, 13–16), such as the expression of *ZEB1* (17), *OCT4* (18), sex determining region Y-box2 (*SOX2*) (19), *HDGF* (20), and suppressor of cytokine signaling 2 (*SOCS2*) (21).

Distant and multiple organ metastasis seriously reduces the overall survival of cancer patients (22–25). Compelling clues have demonstrated that cancer metastasis involves multiple factors, such as gene mutations, cancer exosomes, cancer local microenvironment and immune selection (26–29). Further, epigenetic modification affects the development, early metastasis, treatment and prognosis of cancers (17, 30–35). RNA methylation provides us with a level of epigenetic regulation beyond

that of DNA methylation and histone phosphorylation or acetylation. Therefore, m⁶A methylation is likely to provide approaches to study and restrain cancer metastasis. Currently, the mechanism of m⁶A methylation on cancer metastasis remains elusive. Herein, we reviewed the progress of m⁶A-related mRNAs and ncRNAs in cancer metastasis, supplemented the profound pathways between methylated RNAs and cancer metastasis, and proposed the clinical value of m⁶A members as cancer biomarkers and therapeutic targets.

DETECTION OF M⁶A MODIFICATION

M⁶A, one of the most ubiquitous epigenetic modification in eukaryotic RNA, plays profound roles in many biological development (36). Therefore, the detection of m⁶A is particularly significant for its functional research. Transcriptome-wide sequencing and high-sensitivity mass spectrometry were applied to map m⁶A modification sites and to detect and quantify modifications. Nanopore sequencing, a new and portable method to detect base modifications, along with well-characterized microbial references could serve as controls in the development and evaluation of future methods for the identification of base modifications from single-molecule sequencing data (37). To achieve rapid and accurate quantitative detection of m⁶A-RNA, some novel electrochemical immunosensors were invented (38–40). Additionally, Xiao et al. have found that m⁶A modifications preferentially occupy genes with CpG-rich promoters, features of which regulate RNA transcript m⁶A (5).

M⁶A MEMBERS: WRITER, ERASER, AND READER

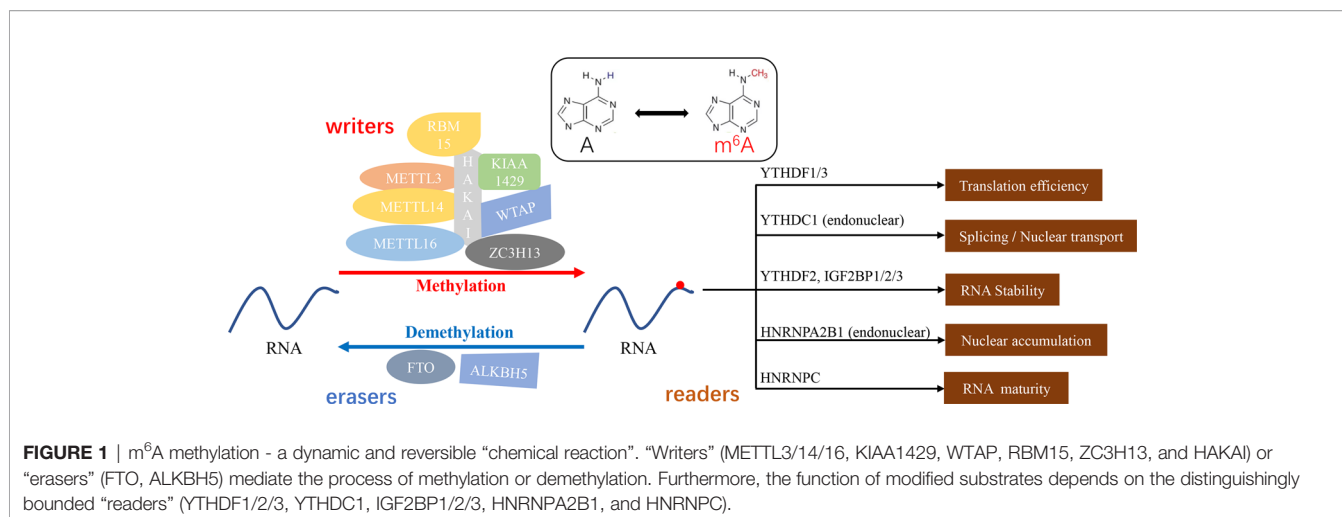
The existing reports of methyltransferases are primarily focusing on methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14) and KIAA1429, which play a dominant role in the regulation between m⁶A methylation and cancer metastasis (17, 41–43). Studies have validated that METTL3 could participate in the fate determination of mRNA, resulting in the remarkable

impact on the embryonic development, cell reprogramming, spermatogenesis, immune cell homeostasis, endothelial cell to hematopoietic cell transformation and so on (11, 44–49). As a synergistic protein of METTL3, METTL14 is not only involved in the biological processes mentioned above, but also attend the self-renewal and differentiation of embryonic stem cells and gametogenesis in mice (50). In cancer, METTL3-mediated methylation leads to epithelial mesenchymal transformation (EMT) and lung or liver metastasis in cancer patients (17, 19, 21, 51). Similar to METTL3, METTL14 was also proved to accelerate the progression of acute myeloid leukemia (AML) (52). KIAA1429 (VIRMA, via-like m⁶A methyltransferase associated) was found to be the largest molecule in the m⁶A methyltransferase complex (53). Silencing KIAA1429 has been reported to attenuate cell proliferation and liver cancer metastasis *in vitro* and *in vivo* (54). In addition, Wilms' tumor-associated protein (WTAP), RNA-binding motif protein 15 (RBM15), Zinc finger CCCH domain containing protein 13 (ZC3H13), HAKAI and methyltransferase-like 16 (METTL16) are also components of methyltransferase complex (43, 55–58) (**Figure 1**).

Known as “erasers”, the demethylases could reverse the action of methyltransferases and make the m⁶A modification flexible and invertible (59). Fat mass and obesity-associated protein (FTO) as well as alkylation repair homing protein 5 (ALKBH5) are the two primary m⁶A erasers to be extensively studied. FTO has been implicated in weight gain and obesity and down-regulation of mRNA transcript levels. The aberrant expression of the FTO showed the enhancing effect on the chemoresistance and glioblastoma stem cell self-renewal (60–62). Niu et al. have proven that FTO could reduce apoptosis in breast cancer cells by inducing BNIP3 mRNA degradation (33). ALKBH5 is a key component in the proliferation and tumorigenesis of glioblastoma stem cells (63). ALKBH5 affects the tumorigenicity of human breast cancer cells and the spermatogenesis and fertility of mice (64, 65). Interestingly, ALKBH5 acts as a profound regulator in the maintenance and differentiation of cancer stem cells (CSCs), which is necessary for the formation and metastasis of primary cancers (65, 66). Moreover, FTO and ALKBH5 have been proposed to inhibit the EMT process. FTO is involved in the inhibition of EMT in intrahepatic cholangiocarcinoma (ICC) (53), and ALKBH5 impairs the migration and invasion of pancreatic cancer. Together, these m⁶A writers and erasers govern different states and processes of cancer metastasis.

Act as m⁶A readers, RNA-binding proteins have been evidenced to specifically select and bind to m⁶A sites (67, 68). YTHDC1 reads m⁶A sequences of mRNA and accelerates mRNA nuclear transport and alternative splicing (69). YTH N⁶-methyladenosine RNA binding protein 1/3 (YTHDF1/YTHDF3) mediated methylation enhances the translation of mRNA. The binding of YTH N⁶-methyladenosine RNA binding protein 2 (YTHDF2) to m⁶A site increases mRNA degradation (21, 70) (**Figure 1**). What's more, m⁶A methylation affects gene expression and cell function (12), such as maintaining the stability of genetic material, establishing epigenetic models, and mediating cellular and embryonic development (71–73).

Abbreviations: M⁶A, N⁶-methyladenosine; M¹A, N¹ atom of adenine; M⁵C, 5-methylcytosine; M⁷G, N⁷-methylguanosine; NcRNAs, non-coding RNAs; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; METTL16, methyltransferase-like 16; YTHDF1/2/3, YTH N⁶-methyladenosine RNA binding protein 1/2/3; EMT, epithelial mesenchymal transformation; FTO, fat mass and obesity-associated protein; ALKBH5, alkylation repair homing protein 5; AML, acute myeloid leukemia; CSCs, cancer stem cells; SOX2, Sex determining region Y-box 2; NSCLC, non-small-cell lung cancer; EOC, epithelial ovarian cancer; HBXIP, hepatitis B x-interacting protein; DGCR8, DiGeorge syndrome chromosomal region 8; CarRNAs, chromatin regulatory RNAs; GSCs, glioblastoma stem cells; SOCS2, Suppressor of cytokine signal 2; YTHDC1, YTH domain-containing 1; ZC3H13, Zinc finger CCCH domain containing protein 13; RBM15, RNA-binding motif protein 15; WTAP, Wilms tumor-associated protein; MiRNA, microRNA; HuR, Human antigen R; FOXM1, Forkhead box protein M1; eIF3b, eukaryotic initiation factor 3b; GLUT4, Glucose transporter-4; HUVEC, human umbilical vein endothelial cell; EpCAM, epithelial cell adhesion molecule; ALDH, aldehyde dehydrogenase; CCND1, cyclin D1.



Studies have shown that the inhibition of m⁶A-related enzymes leads to changes such as immune response, development of nervous system and blood system, indicating that m⁶A might be a significant modification in humans and interfere with the biological function (42, 74–76). Nevertheless, the specific mechanism remains to be further studied.

INSIGHTS OF M⁶A IN CANCER METASTASIS MECHANISMS

Local infiltration and distant metastasis are the primary biological features of multiple malignancies and the leading cause of death (19, 77–79). Cancer metastasis refers to the process in which malignant cells spread to other parts to continue for growth after interacting with host cells, mainly including cell stemness formation (80), environmental angiogenesis or micro-angiogenesis (81), excessive glycolysis (82) and EMT transformation (83) (Figure 2). Extensive findings suggest that m⁶A-related enzymes or proteins affect tumorigenesis (76), proliferation (84, 85), progression (86, 87) and metastasis (88, 89) in various mechanisms. Here, we emphasize the effects of different m⁶A-related molecules on cancer metastasis (Table 1).

m⁶A Methylation and EMT

EMT occurs in a variety of physiological and pathological conditions and is driven by a conservative set of induction signals, transcriptional regulators and downstream effectors (94). Cells exhibit enhanced fibroblast-like morphology and migration capability during EMT (94, 95). A recent report demonstrated that deletion of METTL3 impairs m⁶A and weakens the migration, invasion and EMT of hepatocellular carcinoma (HCC) cells *in vitro* and *in vivo* (60). In colorectal cancer (CRC), a novel lncRNA named *RP11* is rich in m⁶A-RIP and regulated by METTL3 (17). The *RP11*/hnRNP A2B1 complex accelerates mRNA degradation of two E3 ligases, *Siah1* (96) and *Fbxo45* (97), and subsequently prevents

proteasomal degradation of the key EMT-related transcription factor ZEB1 (17, 98). Chen et al. stated that METTL14 inhibits CRC malignant process partly through SOX4-mediated EMT and PI3K/Akt signaling (88). Additionally, m⁶A eraser ALKBH5 was down-regulated in pancreatic cancer cells, which could demethylate *KCNK15-AS1* and regulate *KCNK15-AS1*-mediated cell motility and EMT process (56). In sum, m⁶A can indirectly facilitate or alleviate the extent of EMT by modifying EMT-related molecules. In order to improve current clinical strategies and to better predict the prognosis of patients, it seems evident that EMT is an indispensable aspect to be taken into account.

m⁶A Methylation and Glycolysis

Recently, the field of tumor metabolism has received increasing attention. Aberrant metabolism is a biological sign of malignant tumors (81, 99, 100). Glycolysis has been widely validated to influence tumor progression and metastasis in HCC (81), BC (100), Oral squamous cell carcinoma (OSCC) (101) and leiomyosarcoma (102). Lin et al. validated that highly metastatic HCC cell lines display elevated glycolytic capacity (81). *HDGF* mRNA was detected to boost its stability by METTL3 methylation and bounding to m⁶A reader IGF2BP3 (20). Nuclear HDGF activates Glucose transporter-4 (*GLUT4*) and *ENO2* expression, followed by the acceleration of glycolysis in gastric cancer (GC) cells, which subsequently results in liver metastasis (20). Further, secretory HDGF released from the nucleus promotes cancer angiogenesis. The aerobic glycolysis genes, *GLUT4* and *ENO2*, also key glycolytic enzymes, have been reported in head and neck squamous cell carcinoma (103), pancreatic ductal carcinoma (104), and multiple myeloma (105). However, these glycolytic molecules have not been mentioned to be m⁶A modified and perform downstream functions in the head and neck tissue, the pancreatic duct tissue or bone marrow, and further studies are expected.

m⁶A Methylation and Angiogenesis

Angiogenesis is an imbalance between pro-angiogenic factors and inhibitory factors, which leads to the activation and

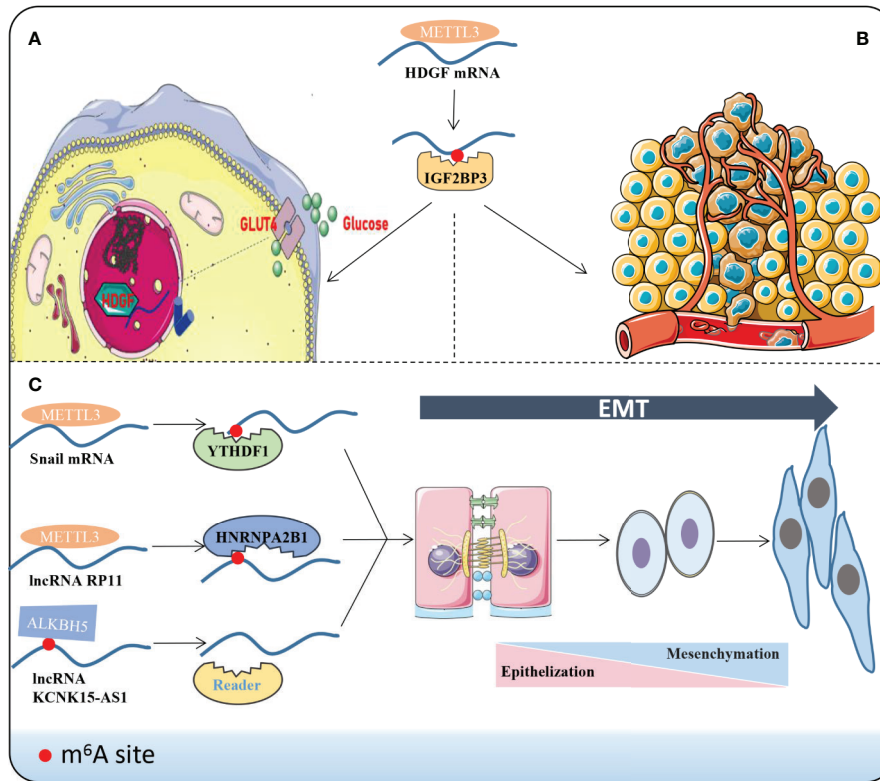


FIGURE 2 | Phenotypic changes induced by m⁶A methylation. For instance, m⁶A reader IGF2BP3 combines the m⁶A sites to improve the stability of HDGF mRNA via METTL3 manner. Subsequently, HDGF accelerates the metabolism and glycolysis (A) of gastric cancer cells and promotes angiogenesis (B). (C) LncRNAs or mRNAs bind to the corresponding “readers” and drive the EMT progression through the m⁶A manner.

overproduction of the vascular system (106). Recently, reports of tumor growth through vascular selection (107) or without the formation of new angiogenesis (108) can be found in the literature. However, solid tumor growth with new blood vessels still dominates. Wang et al. investigated both tube formation and human umbilical vein endothelial cell (HUVEC) growth were significantly increased by overexpressing METTL3 compared with controls *in vitro* (20). Similarly, A negative correlation was found between the expression of *FTO* and *CD34* in ICC (53). *CD34*, a tumor marker involved in angiogenesis, is used as a quantitative indicator of microvascular density (109). Hence, the expression of *FTO* was negatively correlated with local microvascular density (53). Mechanistically, *FTO* reduces the methylation level of *TEAD2* mRNA and impairs the stability of *TEAD2* mRNA and affects angiogenesis (53).

m⁶A Methylation and Cancer Cell Stemness

Acknowledged as a group of cells capable of self-renewal, infinite proliferation and multidirectional differentiation (110), CSCs are the prime origins for the infinite growth of cancers, and the fundamental impetus for the recurrence, metastasis and drug resistance of malignant tumors (111). Through impressing the

expression of CSCs related factors such as *SOX2* (112), *Oct4* (113) and *NANOG* (65, 114), m⁶A modification of mRNA modulates embryonic stem cell pluripotency, and cancer metastasis, recurrence or treatment resistance can be considerably inhibited. Namely, METTL3 actuates CRC cell stemness *in vitro* by maintaining *SOX2* expression and inhibition of METTL3 was associated with markedly decreased CSC surface antigens such as *CD133*, *CD44*, and epithelial cell adhesion molecule (EpCAM) (19). Meanwhile, a decrease in sphere numbers and sizes as well as a strikingly reduced stem cell frequency were observed in METTL3-inhibited CRC cells (19). Exposed to hypoxia stimulated *ALKBH5* overexpression, which reduced the methylation of *NANOG* mRNA and increased the expression of *NANOG* (65). Accordingly, the ability to generate clusters of daughter cells and the activity (115) of aldehyde dehydrogenase (ALDH) 1 activity (116) were significantly enhanced, which indicated the populations of breast cancer cells were enriched in BCSCs (65).

Together, the discovery of m⁶A in metastasis mechanism involves EMT, glycolysis, angiogenesis and cancer cell stemness, which may jointly provide distinguished indicators and drug intervention targets for the individualized diagnosis and medical care.

TABLE 1 | Roles of key m⁶A members in the metastasis of various cancers.

| Writer/ Eraser | Roles | Tumor type | mRNA/ ncRNA | Mechanism and pathway | Reader | Refs |
|-------------------|---------------|-------------------|---|--|------------|------|
| METTL3 | Oncogene | CRC | lnc RP11 | Up-regulates RP11 nuclear accumulation, accelerates Siah1 and Fbxo45 mRNA degradation, prevents ZEB1 degradation, regulates EMT and enhance liver metastasis | HNRNPA2B1 | (17) |
| | | | SOX2 | Stabilizes SOX2 mRNA, induces CRC cell stemness, promotes drug resistance and lung metastasis | IGF2BP2 | (19) |
| | | | pri-miR-1246 | Promotes pri-miR-1246 maturation, down-regulates SPRED2, through MAPK pathway promotes phosphorylation | undetected | (90) |
| | Oncogene | HCC | SOCS2 | Decreases SOCS2 mRNA stability, promotes chronic inflammation and lung metastasis | YTHDF2 | (21) |
| | | | Snail | Activates the translation of Snail, promote EMT | YTHDF1 | (60) |
| | Oncogene | GC | HDGF | Stabilize HDGF mRNA, then HDGF activate GLUT4 and ENO2 expression, accelerates angiogenesis and glycolysis, promotes liver metastasis | IGF2BP3 | (20) |
| Oncogene | NSCLC | @YAP | @Directly enhances YAP translation by recruiting YTHDF1/3 and eIF3b | YTHDF3 | (91) | |
| | | @lnc MALAT1 | @Stabilize MALAT1 mRNA, then MALAT1 sponges miR-1914-3p to promote metastasis through facilitating YAP activity | | | |
| Oncogene | EOC | RHPN1-AS1 | enhances RHPN1-AS1 transcriptional stability, promotes EOC cell viability and mobility | undetected | (89) | |
| | | miR-126 | Enhanced DGCR8 recognition of pri-miR126 and subsequent processing of mature miR-126 | undetected | (92) | |
| METTL14 | Anti-oncogene | HCC | SOX4 | Promote SOX4 mRNA degradation, suppress CRC metastasis through SOX4-mediated EMT process and PI3K/Akt signals | YTHDF2 | (88) |
| | Anti-oncogene | CRC | GATA3 | Promote the degradation of GATA3 pre-mRNA, impairs the binding of HuR to GATA3 pre-mRNA | undetected | (54) |
| KIAA1429 | Oncogene | HCC | GATA3 | Promote the degradation of GATA3 pre-mRNA, impairs the binding of HuR to GATA3 pre-mRNA | undetected | (54) |
| | Oncogene | HCC | GATA3 | Promote the degradation of GATA3 pre-mRNA, impairs the binding of HuR to GATA3 pre-mRNA | undetected | (54) |
| FTO | Oncogene | Breast cancer | BNIP3 | Induces BNIP3 mRNA degradation, inhibit cell apoptosis and promote metastasis | YTHDF2 | (33) |
| | Anti-oncogene | ICC | TEAD2 | Impairs TEAD2 mRNA stability, promotes cisplatin-induced apoptosis, reduces angiogenesis | undetected | (53) |
| ALKBH5 | Oncogene | Breast cancer | NANOG | Under hypoxia stimulation, increases translation of NANOG and enrichment of breast cancer stem cells | undetected | (65) |
| | Anti-oncogene | Pancreatic cancer | KCNK15-AS1 | Upregulate KCNK15-AS1 expression, inhibits cell migration and invasion | undetected | (56) |
| | Anti-oncogene | NSCLC | YAP | Regulates the degradation or translation of YAP mRNA, decreased YAP activity by regulating miR-107/LATS2 axis in an HuR-dependent manner | YTHDF1/2/3 | (93) |

CRC, colorectal cancer; HCC, hepatocellular cancer; GC, gastric cancer; NSCLC, non-small-cell lung cancer; EOC, epithelial ovarian cancer; ICC, intrahepatic cholangiocarcinoma.

PROCEDURE OF M⁶A ON MRNAS AND NCRNAS THROUGHOUT METASTASIS

m⁶A Embellishes mRNA and Is Involved in Cancer Metastasis

Extensive mRNA methylation allows epigenetic modifications to perform a broad scope of functions. Generally, METTL3, as an oncogene, catalyzes m⁶A methylation on mRNAs and facilitates cancers invasion, metastasis, and drug resistance (19–21, 60, 91). Instead, METTL14 primarily pose as an anti-oncogene and contribute to limiting tumor progression (88). As proof, METTL3 mediates insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2)-dependent SOX2 methylation to maintain the expression of SOX2 (19, 19). The expression of genes in the core transcriptional regulatory network associated with SOX2, including cyclin D1 (CCND1) (117), Myc proto-oncogene protein (MYC) (118), and POU5F1 (119), consistently decreased in METTL3-knockdown cells (19). Additionally, SOX2 can form transcription factor complexes with POU5F1. Collectively, METTL3 drives tumorigenesis, cell invasion and chemotherapy resistance of CRC cells might *via* METTL3/SOX2/CCND1-MYC-POU5F1 axis (19). The YTHDF2-dependent pathway makes METTL14 markedly enhanced SOX4 mRNA m⁶A level and elevated mRNA degradation (88). METTL3 not

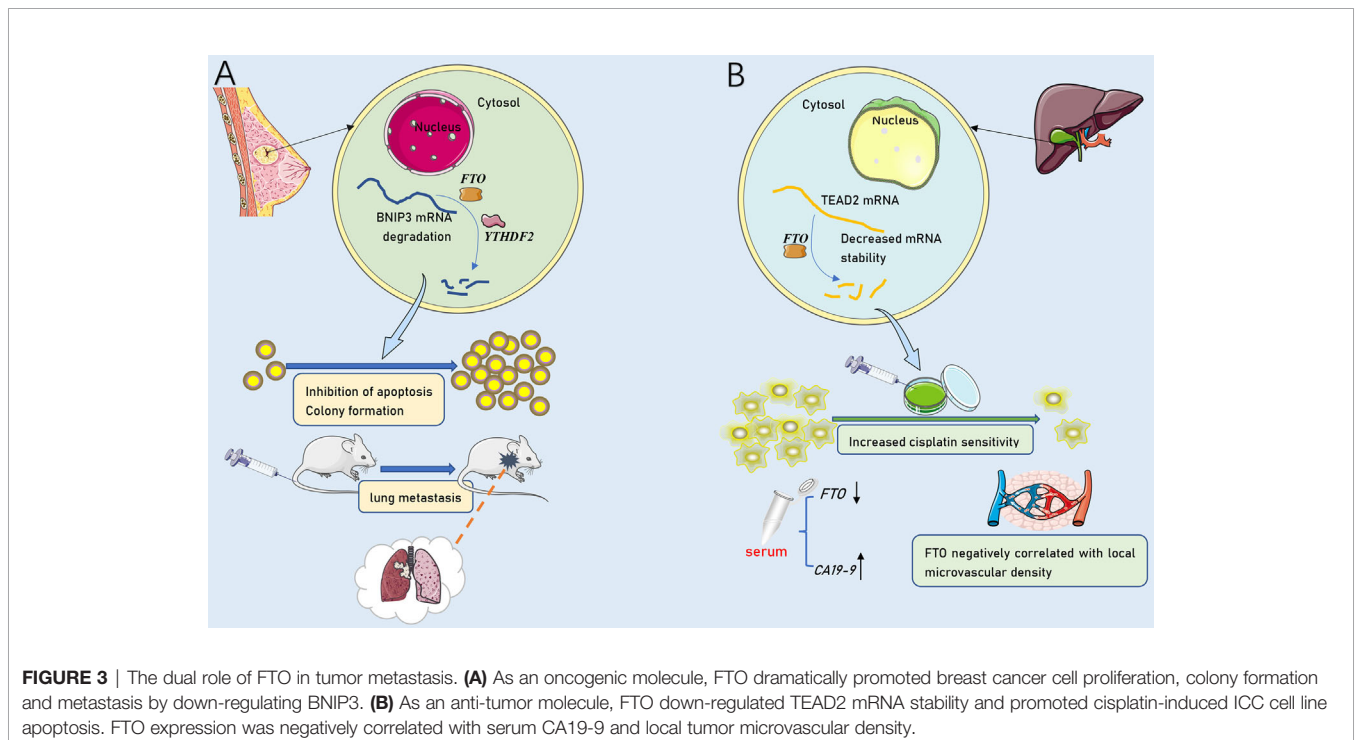
only promotes HCC advancement through YTHDF2-dependent posttranscriptional silencing of SOCS2 (21), but also facilitates CRC progression *via* IGF2BP2-dependent stabilizing of SOX2 mRNA (19). Moreover, METTL3 was involved in boosting the stability of HDGF mRNA by acts on the CDS region (60). Subsequently, m⁶A reader IGF2BP3 directly selects and binds to the m⁶A sites on HDGF mRNA and enhances stability. Evidence implies that the EMT transcription factor Snail can lead to the mass migration of squamous cell carcinoma (120). METTL3-mediated methylation activates SNAIL mRNA translation *via* binding to YTHDF1. Similarly, GATA3 is identified as a direct downstream target of KIAA1429-mediated m⁶A and GATA3 precursor mRNA (pre-mRNA) serves as the substrate (54). GATA3 pre-mRNA degradation is governed by m⁶A modification on GATA3 3'UTR actuated by KIAA1429 (54). GATA3, a member of the GATA transcription factor family, is a recently discovered key factor regulating cell differentiation and cytokine expression, promoting the development of Th2 cells and rendering the body in an immunosuppressed state (121). Interestingly, lncRNA GATA3-AS functions as a cis-acting element for KIAA1429 to interact with GATA3 pre-mRNA (54). In addition, Exposure to hypoxia stimulates ALKBH5 expression, which leads to demethylation of NANOG mRNA capable of encoding pluripotent factors,

increases *NANOG* translation, and advances the percentage of BCSCs (65). FTO mediates the demethylation of *BNIP3* mRNA and promotes self-degradation after binding with the YTHDF2 protein (33). FTO also serves as a cancer suppressor in ICC (53). The inhibition of FTO improves the stability of transcription-enhancing factor *TEAD2* mRNA (122), promotes cisplatin-induced apoptosis, and reduces angiogenesis in ICC cells (53). Notably, the function of m⁶A enzyme can be separate or even opposite in distinct cancers (**Figure 3**). For instance, FTO can not only accelerate the progression of AML (123) and breast cancer (33), but also be treated as an anti-oncogene in ICC (53). There might be more complicated regulatory networks involved in m⁶A demethylation-mediated regulation of cancer metastasis. Recently, a study proposed m⁶A on carRNAs can globally tune chromatin state and transcription, and METTL3 favors chromosome-associated regulatory RNAs (carRNAs) methylation (124). YTHDC1 facilitates decay of a subset of these m⁶A-modified carRNAs, including promoter-associated RNAs, enhancer RNAs and repeats RNAs, through the NEXT-mediated nuclear degradation (124). Therefore, m⁶A might have remarkable functions in the nucleus, which awaited thorough research.

m⁶A Embellishes ncRNA and Is Involved in Cancer Metastasis

Although do not encode RNA, ncRNAs poses as gene monitor, facilitate gene expression (125), and participate in gene activation programs (126) at the levels of transcription, RNA processing and translation (127). Evidence showed that METTL3 heightens the nuclear accumulation of lncRNA RP11 and generates RP11 highly expressed in CRC tissues (17). Clinical

analysis revealed that RP11 considerably upregulates the EMT-related transcription factor ZEB1 (98), triggers EMT and liver metastasis through the RP11/HNRNPA2B1/E3 ligase (Siah1and Fbxo45)/ZEB1 axis, and positively correlated with CRC stage in patients (17). Similarly, it is widely shared that YAP family has a hand in EMT, angiogenesis, and cell proliferation and apoptosis of a variety of cancers, such as CRC (70), non-small-cell lung cancer (NSCLC) (128), and Oral squamous cell carcinoma (OSCC) (129). METTL3/YTHDF3 complex increases the stability of lnc *MALAT1* in an m⁶A manner and *MALAT1* sponges miR-1914-3p to promote *YAP-1* expression (91). There is another reported way by which METTL3 enhances the stability and translation of *YAP* mRNA in NSCLC. *YAP* mRNA is directly identified and combines with YTHDF1/3 and eukaryotic initiation factor 3b (eIF3b) to act on the translation initiation factor and improve the translation efficiency (91) (**Table 1**). Aberrant expression of miRNA in related diseases is caused by the anomalous methylation of the bases in the promoter region of the miRNA gene (130, 131). Wen et al. argued that upregulated METTL3 promotes metastasis of CRC *via* methylates pri-miR-1246, which further promotes the maturation of pri-miR-1246, and the miR-1246/SPRED2/MAPK signaling pathway is involved (90). Another study revealed that pri-miR-126 was transformed into mature miR-126 in a DiGeorge syndrome chromosomal region 8 (DGCR8)-dependent and m⁶A methylation manner (92). Knockdown of ALKBH5 results in the acquisition of m⁶A and reduction the association with Human antigen R(HuR) on the Forkhead box protein M1(FOXM1) transcript. Interestingly, FOXM1AS accommodates the interplay between ALKBH5 and FOXM1 (63). Additionally, lncRNA *RHPN1-AS1*, which contains



METTL3-mediated m⁶A information, may be the reason for the increased stability of *RHPN1-AS1* and high expression in epithelial ovarian cancer (EOC) (89). Since *RHPN1-AS1* acts as ceRNA to antagonize miR-596 and up-regulate LETM1, leading to the metastasis of EOC, METTL3 can be inferred to be the oncogene of EOC *via* m⁶A manner (132). In brief, m⁶A methylation makes sense in epigenetic modification by affecting the translation, stability, degradation and expression of key mRNAs and ncRNAs.

M⁶A MEDIATED METASTASIS IN CANCERS

Digestive System Cancers CRC

Accumulating studies have confirmed that CRC is no longer a single tumor type, and it is more accurate to describe it as a group of heterogeneous diseases due to genetic and epigenetic changes (133). These results led to an increase in CRC typing; the clinical effect of molecular targeted drugs is also unsatisfactory, especially in some patients with distant metastasis. Recently, the epigenetic characteristics of CRC metastasis to the liver and lung were described. METTL14 promotes cancer proliferation and metastasis by promoting the EMT, protein phosphorylation or stemness of cancer cells through downstream targets such as lncRNA RP11 and microRNAs, which greatly improves the distant organ metastasis ability of CRC (17, 19, 90). In addition, CSCs are considered to be the cause of chemotherapy resistance in CRC (134, 135). These studies indicate that m⁶A modification might provide new drug targets for the accurate therapy and early prevention of CRC metastasis.

HCC

Most HCC patients are in an advanced stage at the time of diagnosis and usually accompanied with metastasis (136). At present, combined therapies, including surgery, liver transplantation, interventional and targeted therapy, prolong the survival period of patients with advanced liver cancer to a certain extent (137). However, the 5-year survival rate of HCC patients leaves much to be desired (138). METTL3 impairs the stability of *SOCS2* mRNA and inhibits the chronic inflammation (21). Moreover, the imbalance of METTL3 promotes the occurrence of HCC and chemotherapy resistance by regulating the phosphorylation pathway of METTL3/*SOCS2*/*STAT5*, which refers to key anti-oncogenes at the post-transcriptional level (21). In addition, there is a correlation between the level of methylation modification and the prognosis of HCC patients. Moreover, methyltransferase KIAA1429 acts on the 3'-UTR of *GATA3* pre-mRNA, and the methylated modified RNA binds to HuR protein, which drives malignant phenotypes of HCC (54).

GC

Due to late diagnosis and distant metastasis, the quality of life in GC patients is seriously reduced (139). At present, it is urgent to explore a pleasurable diagnostic and prognostic marker and

treatment target for GC. Recently, Wang et al. argued that m⁶A methylation mediated by METTL3 promotes the m⁶A modification of *HDGF* mRNA, and the m⁶A reader IGF2BP3 directly recognizes and combines the m⁶A site on *HDGF* mRNA to enhance the stability (51). *HDGF* increases glycolysis and angiogenesis in GC cells, which are involved in the progression and metastasis of GC. This suggests that *HDGF* mRNA methylation promotes GC growth and leads to poor prognosis. METTL3, as a carcinogen, might be a new biomarker and therapeutic target for GC.

Pancreatic Cancer

Pancreatic cancer is one of the deadliest cancers in the world. It is usually diagnosed in the terminal stage, and other parts of the body have been metastasized at the time of diagnosis, with poor prognosis (140, 141). At the level of epigenetic regulation, a study of DNA methylation and the stemness of pancreatic cancer cells confirmed the effect of methylation on the metastasis (140). Additionally, studies have shown that ALKBH5, a demethylase, inhibits the invasion and tissue transfer of pancreatic cancer by reducing the methylation level of lncRNA *KCNK15-AS1* (56). The expression level of lncRNA *KCNK15-AS1* is negatively correlated with its methylation level. However, the mechanism between the stability of lncRNA *KCNK15-AS1* and m⁶A methylation is elusive. These mechanisms need to be further studied to find valuable therapies to prevent and control pancreatic cancer.

ICC

ICC is a highly heterogeneous malignant type of HCC (142). Its early clinical symptoms are not easy to perceive, and there is no specific target for clinical detection or treatment (111). Similar to pancreatic cancer, the relationship between ICC and m⁶A methylation has been less reported. Rong et al. found that the protein level of FTO decreased in samples and cell lines of ICC patients. The expression of FTO was negatively correlated with clinical cancer metastasis-related factors, such as cancer local microvascular density and CA19-9 concentration in serum (53) (Figure 3B). Therefore, m⁶A methylation might provide a novel direction for the clinical strategies of ICC treatment.

Female Reproductive System Cancers Breast Cancer

Breast cancer is a malignant and invasive tumor that seriously endangers women's health. It is considered to be the cause of death of approximately 23% of postmenopausal women and is a global problem (143). Although the expression and regulation patterns of target genes related to breast cancer have been extensively studied, little is known about the post-transcriptional regulation mechanisms of gene expression in breast cancer metastatic. The abnormal expression of hepatitis B x-interacting protein (*HBXIP*) drives the proliferation and metastasis of breast cancer. *HBXIP* upregulates METTL14 by inhibiting microRNA(miRNA) *let-7g*. However, METTL14 increases the expression of *HBXIP*, thus forming an *HBXIP/let-7g/METTL14/HBXIP* loop (144). More interestingly, some studies found that METTL14 improves its translation efficiency

without changing the mRNA expression level; that is, the target mRNA abundance remains unchanged (145). Preceding studies suggested that FTO mediates changes in energy metabolism to regulate weight and growth in adults (146, 147). Recent studies found that the expression of FTO is upregulated in human breast cancer. The down-regulation of FTO, knockdown, the proliferation and metastasis of breast cancer tissues and cells were significantly inhibited, while the number of apoptotic cancer cells increased. Further studies confirmed that FTO-mediated m⁶A methylation acts on BNIP3 transcripts that translate apoptotic proteins. Then, YTHDF2 binds to the demethylated *BNIP3* mRNA to inhibit BNIP3-induced apoptosis by reducing the expression of *BNIP3* (33). Accordingly, Niu et al. found that the demethylase FTO acts as an oncogene and promotes the progression of breast cancer through the FTO/BNIP3/Bcl2 anti-apoptosis signaling pathway (33). The study also revealed that the silencing of FTO suppressed lung metastasis in female Balb/c mice. Subsequent studies demonstrated this in mouse models of lung metastasis (Figure 3A). Another study on ALKBH5 found that the exposure of breast cancer cells to hypoxia significantly increased the expression of ALKBH5 in tissues and cells. Then, the demethylation of pluripotent *NANOG* mRNA increased the expression of *NANOG* and induced the enrichment of CSCs (65).

EOC

Recently, lncRNAs have been found in the occurrence, development and metastasis of ovarian cancer (83, 148, 149). lncRNA *DNM3OS* acts as an accelerator in promoting EMT in ovarian cancer (150). A recent report denoted the possibility of *RHPN1-AS1* be used as a ceRNA in the METTL3/*RHPN1-AS1*/miR-596/*LETM1* axis to upregulate the expression of *LETM1* (89). Subsequently, *LETM1* activates the FAK/PI3K/Akt pathway and causes the migration and invasion of EOC cells. The regulation of lncRNA *RHPN1-AS1* by m⁶A modification may provide clues for the discovery of promising diagnostic markers or drug therapeutic targets for EOC patients.

Respiratory System Cancers

NSCLC

Due to the limitations of clinical treatment, there are still no better treatment measures to limit the progression and metastasis of lung cancer. Interestingly, the YAP pathway was reported to promote drug resistance, progression and metastasis of NSCLC (9, 128). *YAP* expression is negatively correlated with ALKBH5 expression and serves as an opposite role in the regulation of cellular proliferation, invasion, migration, and EMT of NSCLC cells (93). ALKBH5 impaired cancer growth and metastasis *in vivo* by decreasing the expression and activity of YAP (93). Meanwhile, the reduction of YAP m⁶A level by METTL3 knockdown inhibits NSCLC growth and enhances sensitivity to DDP *in vivo* (91). The above studies indicate that METTL3 or ALKBH5 might be latent targets for inhibiting the progression and metastasis of NSCLC.

OSCC

OSCC is the most common type of malignant tumor occurring in human oral cavity, with the highest degree of malignancy and the largest head and neck injury, and generally the worst prognosis (129, 151). METTL3-mediated m⁶A modifies the 3' UTR region of *BMII*, which is then recognized by IGF2BP1 and leads to up-regulation of *BMII* translation (152). While, *BMII* serves as an oncogene and targeting *BMII* suppresses cancer growth and prevents relapse (153). Under the catalysis of METTL3, hypermethylation levels promoted the proliferation, self-renewal, migration and invasion of OSCC cells *in vitro*. Hypermethylation have also been proven to attend lung and popliteal lymph node metastasis of OSCC *in vivo*.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is an endemic disease associated with Epstein-Barr virus infection, genetic element and environmental factors in Southeast Asian countries, and is also a high incidence in southern China (154, 155). Easy to relapse and early metastasis are the important barriers in nasopharyngeal carcinoma treatment. In analyzing differentially expressed m⁶A-related genes in 55 NPC patients and 20 control patients, Lu et al. found that upregulation of IGF2BP1 and downregulation of METTL3 were associated with poorer progress-free survival in NPC patients (156). Consensus cluster analysis and risk model predict that METTL3 is a risk factor for NPC metastasis. Additionally, immunohistochemical technique successfully verified the difference of METTL3 expression in NPC tissues (156). Thereby, m⁶A methylation mechanism may be a promising therapeutic target for NPC.

POTENTIAL CLINICAL APPLICATIONS

Theoretically, m⁶A methylation regulators are posed as efficacious pharmacological targets for anti-cancer drug in solving clinical problems. To illustrate, METTL3 gives rise to unfavorable prognosis by maintaining the stable expression of SOX2 in CRC and glioma (19, 157). Similarly, METTL3 activates the transcription regulator Snail translation and promotes EMT by acting on the mRNA coding region (60). A higher METTL3 expression level was positively associated with advanced OSCC stage and poor 5-year overall survival (152). In addition, METTL3 induces resistance to DDP and metastasis by increasing the extent of m⁶A methylation of YAP *in vivo* (91). In brief, reliable data have suggested that METTL3 might be used as a prognostic indicator or as a reference item for diagnosing early metastasis of cancers. Likewise, both the univariate and multivariate Cox regression analysis were indicative of METTL14 was an independent prognostic factor in CRC (88). Moreover, METTL14 acts as one of the indexes reflecting the recurrence-free survival of HCC and the absence of METTL14 is related to the metastasis *in vitro* and *in vivo* (92). Interestingly, METTL14 was responsible for the aberrant methylation modification in HCC, not METTL3 (92).

As previously mentioned, CSCs are considered to be the cause of chemotherapy resistance in CRC (134, 135). SOX2 is a marker of CSCs and has strong carcinogenic and metastatic potential. SOX2 guides stem cell formation and drug resistance in pancreatic cancer and bladder cancer (158). Markedly, Rhein could reversibly bind to FTO catalytic domain and competitively prevent the recognition of m⁶A modification substrates or alleviated the growth of subcutaneous breast cancer in mice, while another FTO inhibitor meclofenamic acid could effectively increase mRNA methylation levels in glioblastoma stem cells (GSCs) and suppress GSC growth (33, 159). Mechanistically, meclofenamic acid is a non-steroidal anti-inflammatory drug that competes with FTO to bind to RNA substrates containing m⁶A modification sites (159). Additionally, the exploration of distinguished FTO inhibitors is considered to be the preferable treatment strategy for BC (160). Collectively, these FTO inhibitors were rarely verified in the human body or in clinical trials. Accordingly, it is of great significance to select appropriate molecular detection targets or specific drugs for early screening, diagnosis, therapeutic intervention and prognosis evaluation of patients in the future.

CONCLUSION

To conclude, m⁶A methylation has a hand in diversified processes of cancer metastasis, such as facilitates EMT (17, 60, 88), sustains cancer cell stemness formation (19, 65), accelerates metabolism and glycolysis (21, 90), and favor angiogenesis (20). Strikingly, the dual effects of FTO (33, 53) and ALKBH5 (56, 65) published so far remind us that m⁶A manner pose as both a propellant and a restrainer in distinct cancers metastasis. Additionally, the presence of m⁶A-related regulators or pathways has been widely demonstrated in the metastasis of various solid tumors, such as digestive tumors (17, 20, 21, 56), female reproductive system tumors (33, 89), and respiratory system tumors (91, 152, 156). This is far from an isolated scenario, as m⁶A methylation regulates migration, invasion and drug resistance by targeting mRNAs and ncRNAs, which makes a profound contribution to the metastasis of malignant tumors. Moreover, with the gradual invention of means such as electrochemical immunoreceptors to detect m⁶A sites, m⁶A modification are likely to have further biological roles to be unearthed.

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Given summarized above, the relationship between m⁶A methylation and cancer metastasis is further complicated and diverse than originally thought, as it cannot be readily concluded that m⁶A-related enzymes hold carcinogenic character only by increasing the extent of methylation modification and vice versa. Likewise, the knowledge of Rhein, the effective FTO inhibitor, competitively prevented the recognition of m⁶A modified substrate by FTO, which alleviated the growth of subcutaneous breast cancer in mice (33). Nevertheless, it is worth noting that the expected clinical drug trials related to m⁶A substitutes or inhibitors remain rarely carried out. m⁶A modulators, once lurking out of sight, are feasible to be used as sensitive biomarkers or effective intervention for early screening or individualized comprehensive therapy in cancer metastasis. Epigenetic regulation based on m⁶A methylation stands a good chance of opening up a novel dimension in cancer research.

AUTHOR CONTRIBUTIONS

ZS, WY, and QK provided direction and guidance throughout the preparation of this manuscript. QD wrote and edited the manuscript. BS, CC, and YG reviewed and made significant revisions to the manuscript. QZ, GW, and JL collected and prepared the related papers. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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