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REVIEW

Emerging Regulatory Mechanisms of N^6-Methyladenosine Modification in Cancer Metastasis

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Abstract

Cancer metastasis is the major cause of cancer-related deaths and accounts for poor therapeutic outcomes. A metastatic cascade is a series of complicated biological processes. N^6-methyladenosine (m^{6}A) is the most abundant and conserved epitranscriptomic modification in eukaryotic cells, which has great impacts on RNA production and metabolism, including RNA splicing, processing, degradation and translation. Accumulating evidence demonstrates that m^{6}A plays a critical role in regulating cancer metastasis. However, there is a lack of studies that review the recent advances of m^{6}A in cancer metastasis. Here, we systematically retrieved the functions and mechanisms of how the m^{6}A axis regulates metastasis, and especially summarized the organ-specific liver, lung and brain metastasis mediated by m^{6}A in various cancers. Moreover, we discussed the potential application of m^{6}A modification in cancer diagnosis and therapy, as well as the present limitations and future perspectives of m^{6}A in cancer metastasis. This review provides a comprehensive knowledge on the m^{6}A-mediated regulation of gene expression, which is helpful to extensively understand the complexity of cancer metastasis from a new epitranscriptomic point of view and shed light on the developing novel strategies to anti-metastasis based on m^{6}A alteration.

Keywords Cancer metastasis · m^{6}A · Epitranscriptomic modification · RNA metabolism · Organ-specific metastasis

Abbreviations

m6A	N6-methyladenosine
m1A	N1-methyladenosine
m3C	3-Methylcytosine
m5C	5-Methylcytosine
m1G	N1-methylguanosine
m7G	7-Methylguanosine
ac4C	N4-acetylcytidine
EMT	Epithelial-mesenchymal transition
VEGF	Vascular endothelial growth factor
HPCs	Hematopoietic progenitor cells
SDF-1	Stromal cell-derived factor-1
MMP-9	Matrix metallopeptidase 9
CTCs	Circulating tumor cells
METTL3	Methyltransferase-like 3
WTAP	Wilms tumor 1-associated protein
FTO	Obesity-associated protein
ALKBH5	AlkB homolog 5
IGF2BP	Insulinlike growth factor 2 mRNAbinding protein family
HNRNPA2B1	Heterogeneous nuclear ribonucleoproteins A2/B1
PRRC2A	Prolinerich and coiledcoilcontaining protein 2A
CNV	Copy number variation
OS	Overall survival
DFS	Disease-free survival
HNSCC	Head and neck squamous cell carcinoma
UCEC	Uterine corpus endometrial carcinoma
ccRCC	Clear cell renal cell carcinoma
DNMT2	DNA methyltransferase-like 2
HCC	Hepatocellular carcinoma
CRC	Colorectal cancer
GC	Gastric cancer
PDAC	Pancreatic ductal adenocarcinoma
CC	Cervical cancer
CSC	Cancer stem cell

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Introduction

Cancer has ranked as the second leading cause of death worldwide, which has become a global burden and threat to human health. Cancer metastasis is the principal cause of high mortality rate, and approximately over 90% of cancer patients die of metastasis. Metastasis is a complex biological process including epithelial–mesenchymal transition (EMT), angiogenesis, intravasation and extravasation, and ultimately metastatic outgrowth. Despite great advances in cancer biology, our current knowledge on cancer metastasis is still poor. At present, there is still a lack of available measures to monitor early metastasis and target cancer metastasis for effective therapy. Therefore, it is necessary to enrich our understanding of the progression of cancer metastasis.

Accumulating evidence demonstrates that cancer cells undergo a series of complicated genetic, epigenetic and epitranscriptomic alterations during the process of metastasis. A variety of genomic variations, such as DNA methylation, histone modifications and chromatin remodeling, have been extensively studied in cancer development. With the advances of next-generation sequencing, RNA modifications, such as N^6-methyladenosine (m^6A), N^1-methyladenosine (m^1A), 3-methylcytosine (m^3C), 5-methylcytosine (m^5C), N^1-methylguanosine (m^1G), 7-methylguanosine (m^7G), and N^4-acetylcytidine (ac4C), have come to prominence and become a hotspot field in cancer (Barbieri and Kouzarides 2020; Roundtree et al. 2017). These highly decorated RNAs with different modifiers are an efficient pathway to regulate gene expression and execute biological functions. Among these chemical RNA modifications, N^6-methyladenosine (m^6A) is the most abundant and conserved epitranscriptomic alteration in eukaryotic cells, which plays a critical role in cancer metastasis.

In this review, we first systematically summarized the mechanisms of how m^6A regulates metastasis in different cancers. Moreover, we also highlighted the limits and perspectives of m^6A-related researches and discussed the potential application of the m^6A axis in cancer diagnosis and therapy.

Cancer Metastasis Is a Complicated Process

Metastasis is the major cause of lethality for cancer patients. Despite the great advances in cancer biology, when and how cancer metastasis occurs remain largely unknown. Cancer metastasis is an extremely complicated process with multiple factors participating in it and multiple pathways being regulated. First, depolarization is triggered and cancer cells undergo EMT, acquiring invasive properties. Next, the cells successively promote angiogenesis for intravasation to the blood vessels. After successfully surviving the attacks in the circulation, the cells go through extravasation, reside on distant organs, and eventually form metastatic lesions (Gao et al. 2019; Obenauf and Massagué 2015; Suhail et al. 2019).

Cancer metastasis is not a random procedure. Clinically, the organ specificity of metastasis has been recognized early. For example, breast cancers have a propensity to metastasize to bone, small cell lung cancers are prone to brain metastasis, and colon cancers prefer to metastasize in the liver. Along this line, metastasis is highly purposeful and selective (Peinado et al. 2017). In 1889, Paget proposed the "seed-and-soil" hypothesis, which suggested that cancer cells (seeds) can live and grow only when they fall on congenial soil (Paget 1889). Based on this observation, numerous researchers have conducted more in-depth studies on the mechanism of organ-specific metastasis, and proposed that metastasis requires the coordination of cancer cells and the microenvironment. During the process, cancer cells not only gradually adapt to the new microenvironment, but also modify the environment via complex interaction through cytokines, metabolites or certain phenotypical features (Bos et al. 2009; Hoshino et al. 2015; Jin et al. 2020b; Kaplan et al. 2005). Previous analyses have indicated that the subtypes with different histological or molecular characteristics tend to colonize at different locations (Fumagalli et al. 2020; Laughney et al. 2020). The dynamic bidirectional process may be the essence of organ-specific metastasis. In addition to the famous "seed-and-soil theory", Kaplan et al. first proposed the "pre-metastatic niches" hypothesis in 2005, which suggested that primary tumors induce the formation of pre-determined microenvironments in distant sites to facilitate survival and proliferation of the unreached cancer cells (Kaplan et al. 2005). For instance, the soluble factor, vascular endothelial growth factor (VEGF), is released from the primary tumor and then enters into the circulatory system. After arriving at the remote target organ, VEGF induces the inherent fibroblasts to produce fibronectin, which can mobilize and recruit $VEGFR^+VLA\text{-}4^+$ hematopoietic progenitor cells (HPCs) to the target organ. In this microenvironment, the HPCs interact with the fibroblasts and increase the expression of stromal cell-derived factor-1 (SDF-1) and matrix metallopeptidase 9 (MMP-9). SDF-1 promotes the adhesion of $CXCR4^+$ circulating tumor cells (CTCs) at the target site, while MMP-9 is beneficial for remodeling the local microenvironment to make it more suitable for the colonization and growth of CTCs (Kaplan et al. 2005). Subsequently, with the efforts of the researches, some other tumor-derived soluble factors, membrane vesicles, exosomes, and recruited bone marrow-derived cells with functions in line

with the "pre-metastatic niches" hypothesis have been successively identified and further confirmed (Liu et al. 2016b; Murgai et al. 2017; Olmeda et al. 2017; Zeng et al. 2018). The new concept is consistent with the previous "seed-and-soil" hypothesis, but it extends a more dynamic perspective of metastasis that cancer cells have not yet arrived at the target lesions. In this concept, the primary tumor sends special envoys to the specific site, catalyzing the formation of a specific "soil" (pre-metastatic niche), which determines the adhesion, colonization, and growth of CTCs and becomes the critical "speed-limiting" node for the formation of target organ metastases.

Recently, tumor dormancy, highly consistent with the "seed-and-soil" hypothesis, has been emphasized in metastasis by numerous researchers (Phan and Croucher 2020). As early as 1954, Hadfield used the term "dormancy" to describe malignant cancer cells that survive for a long time without significant proliferation (Hadfield 1954). The definition of tumor dormancy covers two scenarios: a solitary cell that enters the G0 phase to undergo cell cycle arrest; or a small cluster of cells having a constant population due to an equal rate of proliferation and apoptosis (Phan and Croucher 2020). Although the two scenarios are more or less the result of the interaction between the tumor and its microenvironment, single-cell dormancy that remains dormant or non-proliferating in unsuitable soil is more consistent with the "seed-and-soil" hypothesis. However, unlike the static perspective proposed by Paget (Paget 1889), dormant cells, after going through the incubation period, can be reactivated and proliferate to metastasize with clinical manifestations (Correia et al. 2021; Vera-Ramirez et al. 2018).

Many studies have indicated that cancer cells undergo a series of complicated genetic, epigenetic and epitranscriptomic alterations during metastasis, such as the well-known genomic variations, DNA methylation, histone modifications and chromatin remodeling (Audia and Campbell 2016; Calabrese et al. 2020; Jones et al. 2016; Klutstein et al. 2016; Koch et al. 2018). Recently, epitranscriptomic alterations, especially the m^6A modification of RNA, have become a novel scientific hotspot in the cancer metastasis field.

Critical Components of the m^6A Modification Machinery

There are hundreds of chemical modifications that have been identified in RNA, such as N^1-methyladenosine (m^1A), N^6-methyladenosine (m^6A), 5-methylcytosine (m^5C), 3-methylcytosine (m^3C), N^1-methylguanosine (m^1G), N^7-methylguanosine (m^7G), N4-acetylcytidine (ac4C) (Barbieri and Kouzarides 2020). With the improvement of high-throughput sequencing approaches, the m^6A decoration has become the best characterized epitranscriptomic alteration at present (Barbieri and Kouzarides 2020).

It is reported that m^6A is the most abundant and conserved RNA modification in eukaryotic cells. This type of RNA modification is catalyzed by an installed m^6A machinery composed of multiple methyltransferases, demethylases and m^6A-binding proteins (He et al. 2019). Methyltransferases are usually called as "writers" that are responsible for methylating the N^6 of adenosine. At present, the well-studied m^6A writers contain methyltransferase-like 3 (METTL3), METTL14, METTL16, Wilms tumor 1-associated protein (WTAP), RBM15/15B and KIAA1429. The m^6A modification is a dynamic and reversible process that can be removed by specific RNA demethylases, such as fat mass and obesity-associated protein (FTO) and alkB homolog 5 (ALKBH5). Herein, FTO and ALKBH5 are also termed as "erasers" of m^6A. The functions and mechanisms of m^6A modifications are usually recognized and deciphered by various m^6A RNA-binding proteins called "readers". Many protein family members have been identified as m^6A "readers", such as the members of YTH domain-containing family (YTHDFs and YTHDCs), insulin-like growth factor 2 mRNA-binding protein family (IGF2BP), eukaryotic initiation factor EIF3, heterogeneous nuclear ribonucleoproteins A2/B1 (HNRNPA2B1) and prolinerich and coiledcoilcontaining protein 2A (PRRC2A). YTH domains can directly bind to the m^6A site of the RNA, and the other readers may bind to the surrounding unfolded RNA. The "writer–eraser–reader" system of m^6A can determine the fate of the target RNA through regulating its transcription, processing, splicing, RNA stability and translation. The m^6A regulation is described in Fig. 1.

There are some genomic alterations on m^6A regulators. In hepatocellular carcinoma, we have reported that m^6A regulator genes undergo a prevalent alteration of copy number variation (CNV) via analyzing the TCGA database. *YTHDF3*, *CBLL1*, *IGF2BP1/3*, *HNRNPA2B1*, *KIAA1429*, and *YTHDF1* are found to display high frequency of CNVs in HCC (Shen et al. 2020). Wang et al. reported that HCC patients with any mutation of the m^6A regulators may suffer from shorter overall survival (OS) and disease-free survival (DFS) (Wang et al. 2020d), and *METTL16* or *ALKBH5* deletion may predict poor OS and DFS in HCC (Wang et al. 2020d). In some other tumors, such as head and neck squamous cell carcinoma (HNSCC), uterine corpus endometrial carcinoma (UCEC), clear cell renal cell carcinoma (ccRCC) and bladder urothelial carcinoma, m^6A regulators are characterized by rare somatic mutations. Although most of the writer and eraser genes tend toward loss of copy number in HCC and HNSCC, the reader genes, such as *YTHDC1*, *YTHDC2*, *YTHDF3* and *IGF2BP2,* tend toward gain of copy number in HNSCC, UCEC and ccRCC (Wang et al. 2021b; Wang et al. 2020g; Zhou et al. 2019; Zhou et al. 2020). However, whether these genomic alterations might contribute to

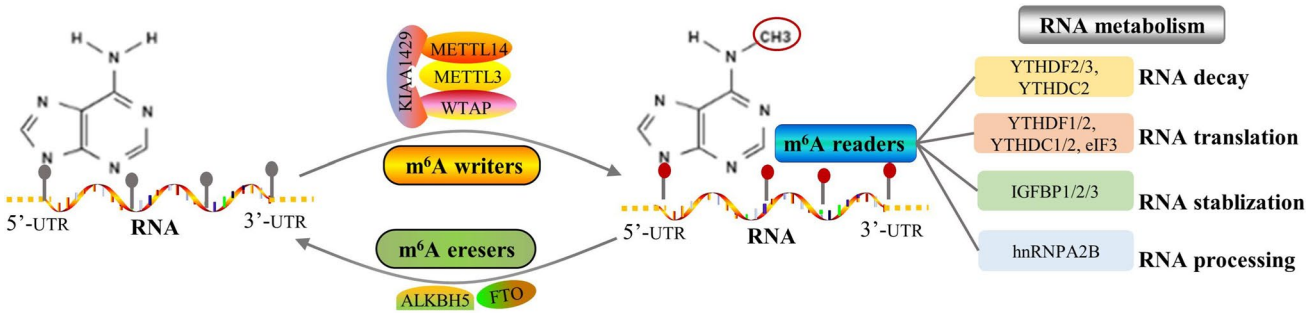


Fig.1 The regulatory machinery of m^{6}A modification. The diagram showed the m^{6}A machinery. The m^{6}A writers mainly contain METTL3, METTL14, WTAP and KIAA1429, which are responsible for methylating at the N^6 position of adenosine. The m^{6}A eraser is composed of RNA demethylases such as FTO and ALKBH5 to remove m^{6}A modification from target RNAs. The m^{6}A reader is essential to recognize and decipher m^{6}A modification, which may determine RNA fate to undergo decay, translation, RNA stabilization or RNA processing. The well-documented m^{6}A readers include YTHDF1/2/3, YTHDC1/2/3, IGF2BP1/2/3, and hnRNPA2B1

aberrant expression and dysfunctions of these m^{6}A regulators needs to be further illustrated.

In contrast to the m^{6}A, the other modifications of RNA have not been extensively studied due to the limitation of sequencing methods and the lack of specific antibodies. For instance, the m^{1}A modification, which is mainly found in tRNA and rRNA but few in cytosolic mRNA, usually depends on TRMT10A and TRM61 complex to add methyl group. The YTH protein family is involved in recognizing the m^{1}A modification, whereas ALKBH1 and ALKBH3 are responsible for removing the methyl group (Chen et al. 2019; Dai et al. 2018; Liu et al. 2016a; Saikia et al. 2010). The m^{5}C is found in a wide range of RNAs, including rRNA, tRNA, mRNA, ncRNA and enhancer RNA. Recent investigation showed that the m^{5}C, especially in tRNA, mainly functions as a structural stability regulator to promote translation accuracy (Yang et al. 2017). NSUN family members (NSUN1 to NSUN7) and DNA methyltransferase-like 2 (DNMT2) are involved in m^{5}C methylation, and ALYREF accounts for binding and recognizing the modification, but which serves as the eraser of m^{5}C remains largely unknown. As for the m^{3}C modification, there are four m^{3}C methyltransferase-like proteins (METTL2A, METTL2B, METTL6, and METTL8) and two m^{3}C demethylases (ALKBH3 demethylating tRNAs and ALKBH1 demethylating mRNA) that have been reported (Cui et al. 2021). The m^{1}G alteration is found mainly in eukaryotic tRNAs, and is frequently catalyzed by Trm5 and Trm10 at the position 37 and at the position 9, respectively (Jin et al. 2019b). The m^{7}G is identified in mRNA, tRNA and rRNA, and may participate in the cap structure formation and protein translation (Barbieri and Kouzarides 2020). Alexandrov et al. found that m^{7}G on tRNA is triggered by the METTL1-WDR4 complex, while m^{7}G in rRNA is mediated by WBSCR22 protein (Alexandrov et al. 2002; Haag et al. 2015). The readers and erasers of m^{7}G need to be further elucidated (Ramanathan et al. 2016). In addition to the methylation on RNAs, the ac4C modification is the first acetylation event that is found in mRNA, and successively reported in tRNAs and rRNAs. And it is catalyzed by a single enzyme NAT10. A recent study addressed that the ac4C on mRNA can promote mRNA stability and enhance the translation efficiency (Arango et al. 2018).

Accumulating evidence has demonstrated that the m^{6}A machinery plays important roles in several physiological and pathological pathways, which have been extensively investigated in embryogenesis, neurogenesis and cancer development (He et al. 2019; Yoon et al. 2017; Zhao et al. 2017). Some of the components of the m^{6}A machinery have promising potentials for clinical translation to become ideal diagnostic biomarkers and therapeutic targets. In this review, we mainly focus on the regulatory functions and mechanism of m^{6}A in cancer metastasis.

The Functions and Mechanisms of m^{6}A Modification in Metastasis of Various Cancers

M^{6}A Modification and Hepatocellular Carcinoma Metastasis

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide with high incidence and mortality. Metastasis accounts for the majority of deaths in HCC. The m^{6}A modification plays an essential role in the metastasis of HCC.

The m^{6}A writer METTL14 is downregulated in HCC, especially in the metastatic samples. METTL14 can form a complex with the microprocessor protein DGCR8 to regulate m^{6}A-dependent *miR-126* processing, which inhibits HCC metastasis (Ma et al. 2017). Another study showed that EGFR is the direct target of METTL14. METT14 can block EGFR/PI3K/AKT signaling axis to suppress

EMT, metastasis and invasion of HCC (Shi et al. 2020b). KIAA1429 is another critical methyltransferase involved in m^{6}A modifications. KIAA1429 promotes tumor growth and metastasis by downregulating GATA3 expression in HCC. Mechanistically, KIAA1429 can disassociate HuR from *GATA3* pre-mRNA by inducing m^{6}A modification at the 3' UTR, destabilizing *GATA3* pre-mRNA and reducing translation. Moreover, *lncRNA GATA3-As*, derived from the antisense *GATA3* transcript, facilitates the association between KIAA1429 and *GATA3* pre-mRNA, which further enhance the pro-metastatic capacity of KIAA1429 (Lan et al. 2019). *CircDLC1* is another target of KIAA1429-mediated m^{6}A in HCC, which inhibits metastasis via abolishing the interaction between HuR and *MMP1* mRNA, thus reducing MMP1 expression (Liu et al. 2021).

The m^{6}A readers from the YTHDF protein family are widely involved in HCC metastasis. For instance, YTHDF1 binds to m^{6}A-modified *ATG2A* and *ATG14* mRNAs to increase their translation, thereby inducing autophagy and metastasis under hypoxia (Li et al. 2021a). A recent study reported that sublethal heat stress can elevate m^{6}A binding near the 5'UTR of the *EGFR* mRNA, which facilitates the association of YTHDF1 to improve EGFR protein output. The activation of the m^{6}A-YTHDF1-EGFR axis contributes to HCC metastasis after insufficient radiofrequency ablation treatment (Su et al. 2021). The other homolog, YTHDF2, modulates m^{6}A binding at 5'UTR of the *OCT4* mRNA to augment OCT4 translation, thus sustaining cancer stem cell properties and promoting metastasis in HCC (Zhang et al. 2020a). Wang et al. demonstrated that YTHDF3 can stabilize *Zeb* mRNA to induce HCC cell migration in an m^{6}A-dependent manner (Wang et al. 2020c).

The m^{6}A erasers also extensively participate in HCC metastasis via inducing mRNA demethylation. For example, FTO can modulate the m^{6}A demethylation of cancer stem cell (CSC)-related genes including *SOX2*, *KLF4* and *NANOG*, which increases the expressions of these genes to maintain stemness and metastasis (Bian et al. 2021). The upregulated oncoprotein AMD1 stabilizes the interaction between *IQGAP1* and FTO, to prevent ubiquitination-mediated degradation of FTO, thereby enhancing HCC metastasis (Bian et al. 2021).

M^{6}A Methylation and Colorectal Cancer Metastasis

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths because of the high rate of metastasis and recurrence (Bray et al. 2018). Emerging investigations indicate that m^{6}A modification and regulators exert pivotal roles in modulating the metastasis of CRC.

Similar to HCC, the m^{6}A writer METTL14 is dramatically downregulated in CRC, which is associated with shorter survival. METTL14 mediates m^{6}A methylation of *SOX4* mRNA and facilitates the degradation of m^{6}A-*SOX4* mRNA in a YTHDF2-dependent manner. SOX4 has an oncogenic capacity to drive EMT and migration by activating the PI3K/AKT signaling pathway. Decreased expression of METTL14 markedly promotes invasion and migration of CRC via increasing SOX4 expression (Chen et al. 2020a). This study also found that histone demethylase KDM5C-mediated demethylation of H3K4me3 at the METTL14 promoter may account for the low transcription of METTL14 in CRC (Chen et al. 2020a). Another study reported that MeCP2 can associate with METTL14 to decrease m^{6}A modification of the tumor suppressor *KLF14* mRNA, thus reducing KLF14 expression and promoting CRC metastasis (Wang et al. 2021a). MTTL14 can mediate m^{6}A modification of non-coding RNA, as well as coding mRNAs, in CRC progression. For example, low expression of METTL14 remarkably abolishes m^{6}A deposition of *lncRNA XIST* and increases XIST expression to promote tumorigenicity and metastasis of CRC cells (Yang et al. 2020a). METTL14 can modulate the processing of *miR-375* via m^{6}A methylation, thereby increasing the expression of *miR-375* targets, including YAP1 and SP1 to facilitate the metastasis of CRC (Chen et al. 2020b).

METTL3 serves as an important m^{6}A writer that is frequently upregulated in CRC and promotes metastasis via m^{6}A methylation (Hou et al. 2021a; Li et al. 2019). *SOX2* and *HMGA1* are the targets of METTL3. The m^{6}A reader, IGF2BP2, can recognize m^{6}A-*SOX2* RNA and m^{6}A-*HMGA1* to increase their protein output, thereby driving CRC metastasis (Hou et al. 2021a; Li et al. 2019). Additionally, METTL3 can induce *circ1662* expression by increasing m^{6}A modifications in its flanking region. *Circ1662* can bind to YAP1 and accelerate its nuclear accumulation to increase SMAD3 expression, thereby promoting invasion and migration of CRC (Chen et al. 2021a). Wu et al. reported that m^{6}A-induced *lncRNA RP11* mediates the dissemination of CRC cells (Wu et al. 2019). METTL13 is responsible for the m^{6}A deposition and the demethylase ALKBH5 can reduce RP11 expression. The m^{6}A reader hnRNPA2B1 forms a complex with *lncRNA Rp11* and other target mRNAs, such as two E3 ligases *Siah-1* and *Fbx45* mRNAs, and subsequently reduces their translation. As a result, ZEB1 is protected from ubiquitin-mediated degradation by E3 ligases Siah-1 and Fbx45 to trigger metastasis (Wu et al. 2019).

M^{6}A Modification and Gastric Cancer Metastasis

Gastric cancer (GC) is characterized as one of the most invasive malignancies, ranking as the third most deadly cancer worldwide (Bray et al. 2018). The regulatory roles of m^{6}A modification in GC metastasis have attracted increasing attention.

The m^{6}A writer METTL3 has been extensively studied in GC metastasis and progression. The oncogene *ZMYM1* was identified as a target of METTL3 for m^{6}A modification, and the m^{6}A-*ZMYM1* mRNA is recognized by the reader HuR to enhance its stability and argument translation. ZMYM1 recruits CtBP/LSD1/CoREST transcriptional complex to repress E-cadherin expression, and thus induces EMT and metastasis in GC (Yue et al. 2019). Recently, Wang et al. revealed that METTL3 was involved in tumor growth and liver metastasis of GC (Wang et al. 2020e). Mechanistically, METTL13 modulates m^{6}A deposition of *HDGF* mRNA, and the reader protein IGF2BP3 enhances *HDGF* mRNA stability to increase the protein expression. The secreted HDGF facilitates angiogenesis, while the nuclear HDGF transcriptionally activates glycolysis by driving GLUT4 and ENO2 expression (Wang et al. 2020e). In addition to increasing oncogene expression, METTL3 decreases tumor suppressor gene expression levels. The tumor suppressor BATF2 interacts with and improves P53 protein stability to inhibit ERK phosphorylation and activation. METTL3 reduces BATF2 expression in an m^{6}A-dependent pathway, thereby activating the ERK pathway and inducing metastasis of GC (Xie et al. 2020b). Of note, some upstream regulators are responsible for METTL3 activation in GC. For instance, P300-mediated H3K27 acetylation within the METTL13 promoter region can trigger its transcription (Wang et al. 2020e). *MiR-338-5p* targets METTL3 reduction to inhibit metastasis, but *miR-388-5p* frequently undergoes methylated silence by EED in GC progression (Zhang et al. 2021).

Besides m^{6}A readers HuR and IGF2BP3, high-expressed reader YTHDF1 also participates in metastasis of GC and indicates poor prognosis and shorter survival time (Chen et al. 2021d). YTHDF1 can facilitate *USP14* translation via the m^{6}A-modification, thereby inducing tumor growth and metastasis (Chen et al. 2021d).

The m^{6}A erasers ALKBH5 and FTO exert vital roles in promoting metastasis of GC. ALKBH5 can bind to and demethylate m^{6}A modification of the *lncRNA NEAT1*, which increases the expression of the oncogene *EZH2* to facilitate metastasis in GC (Zhang et al. 2019). A recent study reported that WNT7B reduces FTO expression to elevate *TCF7L2* mRNA expression in an m^{6}A-dependent manner, stimulating the Wnt/β-catenin signaling axis to reinforce *WNT7B* expression (Gao et al. 2021). The positive feedback loop WNT7B/m^{6}A-TCF7L2/β-catenin pathway firmly promotes GC cancer progression and metastasis (Gao et al. 2021).

M^{6}A Deposition and Pancreatic Cancer Metastasis

Pancreatic cancer is one of the most lethal cancers with a 5-year survival rate of no more than 5% (Bray et al. 2018). The m^{6}A deposition is markedly increased in 70% of the pancreatic cancer specimens and exerts critical roles in regulating metastasis (Wang et al. 2020b).

The m^{6}A writer METTL14 is upregulated and stimulates tumor growth and metastasis in pancreatic cancer. Further studies indicated that METTL14 mediates the m^{6}A modification of *PERP* to accelerate mRNA turnover and decrease PERP protein level, thereby aggravating cancer metastasis and progression (Wang et al. 2020b). The reader YTHDC1 inhibits tumorigenesis and metastasis through the *miR-30d*/RUNX1/SLC2A/HK pathway in pancreatic cancer (Hou et al. 2021b). Mechanistically, the downregulation of YTHDC1 reduces the biogenesis of *miR-30d* in an m^{6}A-dependent manner, and thus triggers the RUNX1-induced Warburg effect to induce tumor growth and metastasis in pancreatic cancer (Hou et al. 2021b). The m^{6}A eraser ALKBH5 is downregulated in pancreatic cancer, which can inhibit motility via demethylating the *lncRNA KCNK15-AS1* (He et al. 2018).

A recent study found that aberrant alternative splicing can regulate m^{6}A activation in pancreatic ductal adenocarcinoma (PDAC) (Chen et al. 2021c). CLK1 kinase mediates the phosphorylation of SR-like splicing factors5$^{250-Ser}$ (SRSF5$^{250-Ser}$), which suppresses METTL14 ^{exon10} and Cyclin L2 $^{exon6.3}$ skipping events. The aberrant splicing granted high METTL14 stronger activity to enhance m^{6}A modifications and facilitate metastasis. Meanwhile, the aberrant Cyclin L2 splicing promotes proliferation and tumor growth in PDAC (Chen et al. 2021c).

M^{6}A Methylation and Breast Cancer Metastasis

Breast cancer has become the second leading cause of cancer-associated mortality among women worldwide (Bray et al. 2018). The 5-year survival rate of metastatic breast cancer patients is only approximately 25%. Breast cancer prefers to metastasize to lung and brain. The roles of m^{6}A modification in breast cancer metastasis have been extensively investigated.

In a breast cancer cell model with a high potential of lung metastasis, the m^{6}A writer METTL3 displays increased expression, whereas the m^{6}A eraser FTO is downregulated (Chen et al. 2021b). KRT7 was identified as the critical effector of m^{6}A-mediated lung metastasis of breast cancer. A mechanistic study demonstrated that METTL3 induces m^{6}A methylation at the A877 residue of *KRT7-AS*, which stabilizes the *KRT7-AS* and *KRT7* mRNA duplex via IGF2BP1/HuR complexes. Additionally, the downregulation of FTO enhances the methylation of the A950 residue at the exon 6 of *KRT7* to promote translation elongation by recruiting YTHDF1 and eEF1 factors toward *KRT7* mRNA (Chen et al. 2021b). The cancer stem cell regulator SOX2 is the downstream effector of METTL3 in breast cancer as well (Xie et al. 2021). METTL3 induces m^{6}A deposition of the *SOX2*

mRNA and increases its protein production via the IGFBP2 reader, which enhances the cancer stem cell properties and promotes invasion and migration of breast cancer (Xie et al. 2021). In contrast to the aforementioned upregulatory and oncogenic roles of METTL3, Shi et al. found that METTL3 is downregulated in breast cancer, which decreases the m^{6}A level of *COL3A1* and increases its expression, leading to metastasis of breast cancer cells (Shi et al. 2020a). These controversial results may be attributable to the highly heterogeneous characterization and different subtypes of breast cancer.

The m^{6}A reader YTHDF3 exerts an important role in modulating the interplay of cancer cells with the brain microenvironment and ultimately leads to brain metastasis (Chang et al. 2020). Mechanistically, the upregulation of YTHDF3 promotes the translation of metastasis-related factors, including *ST6GALNAC5*, *GJA1*, and *EGFR*, in an m^{6}A-dependent manner. These factors help cancer cells to break the blood–brain barrier, stimulate angiogenesis and grow in brain. The high expression of YTHDF3 in metastatic breast cancer is due to its gene copy number amplification and YTHDF3 self-regulation through m^{6}A-dependent translation at its 5'UTR (Chang et al. 2020).

The m^{6}A erasers ALKBH5 and FTO have impacts on the metastasis of breast cancer. The hypoxia-inducible factor triggers ALKBH5 transcription and expression. Consequently, overexpression of ALKBH5 decreases *NANOG* mRNA methylation at the 3'-UTR and increases NANOG protein levels, which promotes the cancer stem cell properties and aggravates breast cancer progression (Zhang et al. 2016). FTO is upregulated in breast cancer and associated with a poor prognosis. FTO induces the demethylation of tumor suppressor *BNIP3* mRNA in its 3'UTR and triggers its degradation, promoting tumor growth and metastasis (Niu et al. 2019). Additionally, FTO modulates invasion and migration by inhibiting *miR-181b*-targeted silencing of oncogene *ARL5B* (Xu et al. 2020).

M^{6}A Modification and Lung Cancer Metastasis

Lung cancer remains the leading cause of cancer-related deaths and has become a seriously global health problem (Bray et al. 2018). The functions of m^{6}A modification have attracted more and more attention in the metastasis of lung cancer.

The m^{6}A writer METTL3 can promote the biogenesis of precursor *miR-143-3p*, relying on m^{6}A methylation, and *miR-143-3p* is upregulated in the brain metastasis samples of lung cancer (Wang et al. 2019a). M^{6}A-modified *miR-143-3p* decreases VASH1 expression and subsequently protects VEGFA protein from VASH1-mediated proteasome degradation, and thus triggers invasion and angiogenesis, breaking the blood–brain barrier, and promoting brain metastasis of lung cancer (Wang et al. 2019a). A recent study found that METTL3 induces metastasis and chemotherapeutic resistance by facilitating *YAP* mRNA stability and translation in lung cancer (Jin et al. 2019a). Mechanistically, METTL3 can directly initiate m^{6}A modification of *YAP* mRNA and recruit YTHDF1/3 and eIF3b to the translation complex to enhance YAP translation. In addition, METTL3 catalyzes m^{6}A deposition of the *lncRNA MALAT1* to stabilize *MALAT1* mRNA. MALAT1 acts as the competing endogenous RNA to sponge *miR-1914-3p*, thereby increasing *YAP* mRNA stability. The m^{6}A-mediated dual regulation of YAP expression contributes to metastasis and aggravates lung cancer progression (Jin et al. 2019a). Another investigation also confirmed the critical role of m^{6}A in regulating YAP expression to affect lung cancer metastasis (Jin et al. 2020a). This study indicated that the low expression of ALKBH5 reduces m^{6}A modification levels of *YAP* mRNA and decreases *YAP* translation and activation depending on YTHDF2. Moreover, ALKBH5 interacts with HuR to augment LAST2 expression by protecting it from *miR-1914-3p*-mediated degradation, which increases the phosphorylation of YAP and inhibits the activity of the YAP axis, blocking metastasis of lung cancer (Jin et al. 2020a).

The m^{6}A reader YTHDC2 is downregulated in lung cancer and is associated with poor differentiation, lymph node metastasis and advanced TNM stage. YTHDC2 can suppress the proliferation and migration of lung cancer cells (Sun et al. 2020). Li et al. found that the m^{6}A reader YTHDF2 is upregulated in lung adenocarcinoma tissues. YTHDF2 promotes tumorigenesis and metastasis by accelerating AXIN1 decay and consequently activating the Wnt/β-catenin signaling cascade (Li et al. 2021b).

The m^{6}A erasers are involved in the metastasis of lung cancer. For instance, FTO can enhance NELL2 expression to trigger metastasis by declining E2F1 m^{6}A modification levels in lung cancer (Wang et al. 2021c). Guo et al. demonstrated that ALKBH5-mediated low m^{6}A level facilitates the maintenance of the stability of *UBE2C* mRNA. The oncogenic UBE2C induces metastasis by repressing autophagy (Guo et al. 2018).

M^{6}A Modification and Urological Malignancies

The m^{6}A axis plays critical roles in regulating metastasis of urological cancers such as prostate cancer, bladder cancer and renal cell carcinoma.

Prostate cancer has ranked the most common malignancy among men worldwide. Metastasis is the main risk factor leading to high mortality, and about 80% of metastatic prostate cancer cases may present with bone metastasis. Wen et al. found that a high m^{6}A level of the *lncRNA NEAT1* is associated with bone metastasis of prostate cancer (Wen et al. 2020). Investigation of the mechanism indicated that

the *lncRNA NEAT1* may function as a scaffold and bind to CYCLIN1 and CDK19 to phosphorylate Poll at Ser2 in an m^{6}A-dependent manner. The *NEAT1*/CDK19/CYCLUNL1 complex could promote cancer metastasis (Wen et al. 2020). Another *lncRNA PCAT6* was found to be upregulated specifically in prostate cancer specimens with bone metastasis (Lang et al. 2021). METTL3-induced m^{6}A modification and IGF2BP3-dependent m^{6}A recognition leads to the overexpression of PCAT6. Furthermore, PCAT6 interacts with *IGF2BP3* and *IGF1R* mRNA to enhance IGF1R expression and facilitates bone metastasis (Lang et al. 2021). Li et al. reported that METTL3 modulates ITGB1 expression via the m^{6}A-HuR-dependent pathway, which influences the association of ITGB1 with Collagen I to trigger bone metastasis of prostate cancer (Li et al. 2020a).

In bladder cancer, the m^{6}A machinery, including METTL3 and YTHDF2, degrades the m^{6}A-modified mRNAs of tumor suppressors *SETD* and *KLF4*, thereby promoting tumorigenesis and metastasis (Xie et al. 2020a). Gu et al. found that the m^{6}A writer METTL14 is downregulated in bladder cancer tissues and tumor-initiating cells (Gu et al. 2019). Low expression of METTL14 facilitates self-renewal capacity, malignant proliferation, and metastasis through decreasing m^{6}A modification levels of *Notch1* mRNA and increasing its translation (Gu et al. 2019). The m^{6}A eraser FTO is upregulated and modulates tumor growth and metastasis in bladder cancer (Tao et al. 2021). FTO demethylates m^{6}A of the *lncRNA MALAT1* and increases its mRNA stability via the YTHDF2 reader. MALAT1 elevates the expression level of MAL2 by sponging *miR-384* to aggravate bladder cancer progression (Tao et al. 2021).

In renal cell carcinoma, the *lncRNA DMDRMR* binds to m^{6}A reader IGF2BP3 to stabilize m^{6}A-modified mRNAs including *CDK4*, *COL6A1*, *LAMA5* and *FN1*, and increase their protein production. Therefore, *DMDRMR* accelerates tumor growth by increasing CDK expression and coordinates cell invasion and metastasis partially by elevating *FN1* translation in an m^{6}A-dependent manner (Gu et al. 2021). Gu et al. reported that low expression of METTL14 can decrease the m^{6}A modification level of *P2RX6* to augment *P2RX6* expression and thus activate the p-ERK1/2/MMP9 signaling axis, thereby promoting renal cancer development (Gu et al. 2021).

M^{6}A Deposition and the Metastasis of Gynecological Tumors

Cervical, ovarian and endometrial cancers are three common lethal gynecological malignancies. Metastasis is the foremost cause for the poor prognosis and mortality of patients with these cancers. The regulatory roles of m^{6}A modification have been deeply investigated in these gynecological cancers.

Cervical cancer (CC) is the second most prevalent cancer in women worldwide. Yang et al. found that METTL3 mediates the *lncRNA ZAFS1* to sponge *miR-647* in an m^{6}A-dependent manner, and this RNA–RNA interaction modulates tumor growth and metastasis in CC (Yang et al. 2020b). Another *lncRNA GAS5-AS1* is markedly downregulated, which is associated with lymphatic and distant metastasis in CC (Wang et al. 2019b). Further studies showed that *lncRNA GAS5-AS1* can form a ternary complex with GAS5 and the m^{6}A eraser ALKBH5, which decreases the m^{6}A modification levels of the tumor suppressor *GAS5* and blocks *GAS5* RNA decay in a YTHDF2-dependent way (Wang et al. 2019b). These m^{6}A-induced effects confer the anti-metastatic function of *lncRNA GAS5-AS1* in CC (Wang et al. 2019b). A recent study demonstrated that the overexpression of the m^{6}A writer METTL3 is closely linked to lymphatic metastasis in CC (Wang et al. 2020f). Mechanistically, METTL3 can enrich m^{6}A deposition of 3′UTR of *HK2* and recruit the reader YTHDF1 to enhance HK2 expression. The m^{6}A-mediated HK2 elevation promotes the Warburg effect and aggravates cancer progression (Wang et al. 2020f). The m^{6}A eraser FTO is closely involved in the proliferation and migration of CC cells (Zou et al. 2019). FTO interacts with *E2F1* and *Myc* mRNAs to accelerate the translation of these oncogenic transcripts, thereby promoting CC development (Zou et al. 2019).

Ovarian cancer has the highest mortality among gynecological tumors and has become an enormous threat to women's health. The m^{6}A writer METTL3 is upregulated in ovarian cancer and associated with lymph node metastasis and an advanced pathological grade (Liang et al. 2020). METTL3 activates the AKT pathway and promotes cyclin D1 expression (Liang et al. 2020). The m^{6}A reader YTHDF1 is overexpressed in ovarian cancer, which is closely correlated with poor prognosis (Liu et al. 2020b). YTHDF1 recognizes m^{6}A-modified *EIF3C* mRNA and facilitates EIF3C protein output, so as to induce tumorigenesis and metastasis (Liu et al. 2020b).

In endometrial cancer, the m^{6}A eraser FTO mediates demethylation at the 3'-UTR of *HOXB13* mRNA to enhance HOXB13 protein translation, thereby activating the Wnt signaling axis to stimulate invasion and metastasis (Zhang et al. 2020b).

M^{6}A Modification and Metastasis in Other Cancer Types

In addition to the aforementioned cancers, the regulatory functions of the m^{6}A axis have been found in other cancers, such as nasopharyngeal carcinoma, oral squamous cell carcinoma, osteosarcoma and thyroid cancer.

In nasopharyngeal carcinoma, m^{6}A modification is enriched on *lncRNA FAM225A* to increase its RNA stability.

The upregulation of *FAM225A* sequesters *miR-590-3p* and *miR-1275* to elevate ITGB3 expression and activate the FAK/PI3K/AKT signaling pathway, which leads to malignant proliferation and invasion of nasopharyngeal carcinoma (Zheng et al. 2019).

In oral squamous cell carcinoma, high expression of METTL3 is closely correlated with poor prognosis (Liu et al. 2020a). METTL3 mediates the m^{6}A modification at the 3' UTR of *BMI1* mRNA and facilitates *BMI1* translation via IGF2BP1, thereby promoting proliferation, self-renewal and metastasis (Liu et al. 2020a).

The m^{6}A writer WTAP was found to promote cancer progression in osteosarcoma (Lian et al. 2018). WTAP induces m^{6}A enrichment at the 3′UTR of *HMBOX1* mRNA and enhances its expression, which activates the PI3K/AKT pathway to stimulate osteosarcoma growth and metastasis (Lian et al. 2018).

M^{6}A modification plays a critical role in regulating thyroid cancer development. Ye et al. reported that the *lncRNA MALAT1* increases the expression levels of the m^{6}A reader IGF2BP2 and Myc by sponging *miR-204* in an m^{6}A-dependent manner, to stimulate migration and invasion of thyroid cancer (Ye et al. 2021). A recent study found that the m^{6}A writer METTL3 is downregulated and markedly associates with poor prognosis in papillary thyroid carcinoma (He et al. 2021). Low expression of METTL3 activates the NF-κb pathway via abolishing the m^{6}A modification of *C-Rel* and *Rel A* and inducing IL-18 secretion to recruit tumor-associated neutrophils, thereby aggravating cancer progression of papillary thyroid cancer (He et al. 2021).

Collectively, the versatile mechanisms of m^{6}A modification in regulating cancer metastasis are summarized in Table1. Additionally, it is well known that cancer stem cell (CSC) maintenance and EMT are two critical events in driving cancer metastasis. The m^{6}A modification plays an important role in regulating the CSC-like properties and EMT process in various types of cancer as mentioned above. Herein, we also summarized the shared common functions of m^{6}A regulators in sustaining CSC-like features and inducing EMT in Fig. 2.

M^{6}A-Mediated Cancer Metastasis Organotropism

It is noteworthy that most cancers are prone to metastasize to a specific organ, known as "organotropism". For instance, colorectal cancer has a high propensity to metastasize to the liver. Breast cancer preferably metastasizes to the lungs, bones and brain. Hepatocellular carcinoma is prone to lung metastasis, whereas prostate cancer frequently relapses in the bone. The specificity of the metastatic process is determined by numerous factors, including tumor-intrinsic properties, organ-specific niches, and the complicated interplay between tumor and the surrounding microenvironment. Increasing evidence demonstrates that m^{6}A modification plays an important role in regulating metastasis organotropism in various cancer.

The liver is one of the most frequently distant metastatic organs in multiple cancers such as colorectal cancer, gastric cancer and pancreatic cancer. In colorectal cancer development, m^{6}A writers, readers and erasers are extensively involved in liver-specific metastasis through the following mechanisms, including METTL14/*XIST*, METTL13/*RP11*, METTL3/*SOX2* and *HMGA1*, METTL14/*miR-375*/ *YAP1* and *SP1*, IGF2BP2/*SOX2* and *HMGA1*, hnRNPA2B1-*Rp11-Siah-1-Fbx45/ZEB1*, and the ALKBH5/*RP11* cascade (Chen et al. 2020b; Wu et al. 2019; Xie et al. 2021; Yang et al. 2020a). In advanced gastric cancer, several m^{6}A pathways greatly contribute to the liver metastasis of gastric cancer including METTL3/BATF2/ERK, METTL3/*ZMYM1*/CtBP/LSD1/CoREST, YTHDF1/*USP14*, METTL3-IGF2BP3/*HDGF*, ALKBH5/*NEAT1*/EZH2, and FTO/*TCF7L2*/Wnt/β-catenin feedback (Chen et al. 2021d; Gao et al. 2021; Wang et al. 2020e; Xie et al. 2020b; Yue et al. 2019; Zhang et al. 2019). In pancreatic cancer, METTL14-mediated *PERP* m^{6}A and YTHDC1-mediated Warburg effect promoted liver metastasis (Hou et al. 2021b; Wang et al. 2020b).

The lung is another favored metastatic site for solid tumors such as HCC, breast cancer, bladder cancer and renal cell carcinoma. There are various m^{6}A factors to trigger lung metastasis of HCC, such as m^{6}A writers METTL14-DGCR8/*miR-126*, METTL14/*EGFR*/PI3K/AKT, KIAA1429/*GATA3*-HuR, and KIAA1429/*CircDLC1*/*MMP1*-HuR, m^{6}A readers YTHDF1/*ATG2A* and *ATG14*, YTHDF1/*EGFR*, YTHDF2/*OCT4*, and YTHDF3/*Zeb*, and m^{6}A erasers FTO/*SOX2*, *KLF4* and *NANOG* (Bian et al. 2021; Lan et al. 2019; Li et al. 2021a; Ma et al. 2017; Shi et al. 2020b; Su et al. 2021; Wang et al. 2020c; Zhang et al. 2020a). In bladder cancer, these m^{6}A-related mechanisms might account for incrased liver metastasis including METTL14/*Notch1*, METTL3-YTHDF2/*SETD* and *KLF4*, YTHDF2/*AXIN1*/Wnt/β-catenin and FTO-YTHDF2/*MALAT1*/*MAL2* (Gu et al. 2019; Li et al. 2021b; Tao et al. 2021; Xie et al. 2020a). In breast cancer, METTL3/*KRT7*, METTL3/*COL3A1*, FTO/*BNIP3*, and FTO-YTHDF1-eEF1/*KRT7* axis are responsible for liver metastasis (Chen et al. 2021b; Niu et al. 2019; Shi et al. 2020a). Gu et al. found that IGF2BP3-induced *FN1* m^{6}A modification contributes to liver metastasis of renal cell carcinoma (Gu et al. 2021).

Lung cancer and breast cancer exhibit great propensity for brain-specific metastasis, and m^{6}A modification is extensively involved in the malignant behaviors. As for the brain metastasis of lung cancer, multiple m^{6}A pathways regulate the process, such as

Table 1 The mechanisms of m^6A regulators in cancer metastasis

m^6A regulators	Functions in Cancer	Target genes	Cancer type	References
Writer METTL14↓	Invasion and migration	*miR-126*	HCC	Ma et al. (2017)
METTL14↓	Migration, invasion and EMT	*EGFR*	HCC	Shi et al. (2020b)
METTL14↓	EMT, invasion and migration	*SOX4*	CRC	Chen et al. (2020a)
METTL14↓	Tumorigenicity and metastasis	*lncRNA XIST*	CRC	Yang et al. (2020a)
METTL14↓	Metastasis	*miR-375*	CRC	Chen et al. (2020b)
METTL14↑	Metastasis and progression	*PERP*	Pancreatic cancer	Wang et al. (2020b)
METTL14↓	Self-renewal capacity, malignant proliferation and metastasis	*Notch1*	Bladder cancer	Gu et al. (2019)
METTL14	Proliferation	*P2RX6*	Renal cancer	Gu et al. (2021)
Writer METTL3↑	Metastasis	*SOX2* and *HMGA1*	CRC	Hou et al. (2021a); Li et al. (2019)
METTL3↑	Metastasis	*KRT7*	Breast cancer	Chen et al. (2021b)
METTL3↑	Stemness, invasion and migratory	*SOX2*	Breast cancer	Xie et al. (2021)
METTL3↑	Metastasis	*COL3A1*	Breast cancer	Shi et al. (2020a)
METTL3	Invasion and migration	*circ1662*	CRC	Chen et al. (2021a)
METTL3↑	EMT, progression and metastasis	*ZMYM1*	GC	Yue et al. (2019)
METTL3↑	Metastasis	*BATF2*	GC	Xie et al. (2020b)
METTL3	Metastasis	A877 residue of *KRT7-AS*	Breast cancer	Chen et al. (2021b)
METTL3↑	Invasion, angiogenesis and metastasis	*miR143-3p*	Lung cancer	Wang et al. (2019a)
METTL3↑	Metastasis and chemotherapeutic resistance	*YAP*	Lung cancer	Jin et al. (2019a, b)
METTL3↑	Progression and metastasis	*MALAT1*	Lung cancer	Jin et al. (2019a, b)
METTL3	Metastasis	*PCAT6*	Prostate cancer	Lang et al. (2021)
METTL3	Metastasis	*ITGB1*	Prostate cancer	Li et al. (2020a)
METTL3	Tumorigenesis and metastasis	*SETD* and *KLF4*	Bladder cancer	Xie et al. (2020a)
METTL3↑	Proliferation and metastasis	*lncRNA ZAFS1*	Cervical cancer	Yang et al. (2020b)
METTL3↑	Progression and metastasis	*HK2*	Cervical cancer	Wang et al. (2020e)
METTL3	Metastasis	*Cyclin D1*	Ovarian cancer	Liang et al. (2020)
METTL3	Proliferation, self-renewal and metastasis	*BMI1*	Oral squamous cell carcinoma	Liu et al. (2020a)
METTL3↓	Progression	*C-Rel* and *Rel A*	Papillary thyroid cancer	He et al. (2021)
Writer METTL13	Glycolysis and angiogenesis	*HDGF*	GC	Wang et al. (2020d)
METTL13	Metastasis	*Rp11*	CRC	Wu et al. (2019)
Writer KIAA1429	Proliferation, apoptosis, invasion and migration	*GATA3*	HCC	Lan et al. (2019)
KIAA1429	Proliferation, invasion and metastasis	*circDLC1*-HuR-*MMP1* axis	HCC	Liu et al. (2021)
Writer WTAP	Proliferation and metastasis	*HMBOX1*	Osteosarcoma	Lian et al. (2018)
Reader hnRNPA2B1	Metastasis	*lncRNA Rp11*, *Siah-1* and *Fbx45*	CRC	Wu et al. (2019)
Reader HuR	EMT and metastasis	*ZMYM1*	GC	Yue et al. (2019)
Reader YTHDF1↑	Autophagy and metastasis	*ATG2A* and *ATG14*	HCC	Li et al. (2021a)
YTHDF1↑	Metastasis	*EGFR*	HCC	Su et al. (2021)
YTHDF1↑	Proliferation and metastasis	*USP14*	GC	Chen et al. (2021d)
YTHDF1↑	Tumorigenesis and metastasis	*EIF3C*	Ovarian cancer	Liu et al. (2020b)

Table 1 (continued)

m^{6}A regulators	Functions in Cancer	Target genes	Cancer type	References
YTHDF1	Progression and metastasis	*HK2*	Cervical cancer	Wang et al. (2020e)
Reader YTHDC1↑	Inhibition of tumorigenesis and metastasis	*miR-30d*/*RUNX1*/SLC2A/HK pathway	Pancreatic cancer	Hou et al. (2021b)
Reader YTHDF2↑	Stemness and metastasis	*OCT4*	HCC	Zhang et al. (2020a)
YTHDF2	Tumorigenesis and metastasis	*AXIN1*	Lung cancer	Li et al. (2021b)
YTHDF2	Tumorigenesis and metastasis	*SETD* and *KLF4*	Bladder cancer	Xie et al. (2020a)
YTHDF2↑	Proliferation and metastasis	*MALAT1*	Bladder cancer	Tao et al. (2021)
Reader YTHDF3↑	Migration	*Zeb*	HCC	Wang et al. (2020c)
YTHDF3↑	Angiogenesis and outgrew	*ST6GALNAC5*, *GJA1*, and *EGFR*	Breast cancer	Chang et al. (2020)
Reader IGF2BP2	Metastasis	*SOX2*, *HMGA1*	CRC	Hou et al. (2021a); Li et al. (2019)
IGF2BP3	Glycolysis and angiogenesis	*HDGF*	GC	Wang et al. (2020d)
IGF2BP3	Metastasis	*PCAT6*	Prostate cancer	Lang et al. (2021)
IGF2BP3↑	Proliferation and metastasis	*lncRNA DMDRMR*	Renal cell carcinoma	Gu et al. (2021)
Eraser FTO↑	stemness and metastasis	*SOX2*, *KLF4* and *NANOG*	HCC	Bian et al. (2021)
FTO	Progression and metastasis	*TCF7L2*	GC	Gao et al. (2021)
FTO↓	Metastasis	A950 in *KRT7* exon 6	Breast cancer	Chen et al. (2021b)
FTO↑	Proliferation and metastasis	*BNIP3*	Breast cancer	Niu et al. (2019)
FTO	Invasion and migration	*miR-181b*	Breast cancer	Xu et al. (2020)
FTO	Metastasis	*E2F1*	Lung cancer	Wang et al. (2021b)
FTO↑	Proliferation and metastasis	*MALAT1*	Bladder cancer	Tao et al. (2021)
FTO	Proliferation and migration	*E2F1* and *Myc* mRNAs	Cervical cancer	Zou et al. (2019)
FTO	Invasion and metastasis	*HOXB13*	Endometrial cancer	Zhang et al. (2020b)
Eraser ALKBH5	Metastasis	*lncRNA NEAT1*	GC	Zhang et al. (2019)
ALKBH5↓	Motility	*lncRNA KCNK15-AS1*	Pancreatic cancer	He et al. (2018)
ALKBH5↑	Stemness and progression	*NANOG*	Breast cancer	Zhang et al. (2016)
ALKBH5↓	Metastasis	*YAP* axis	Lung cancer	Jin et al. (2020a)
ALKBH5↓	Metastasis	*miR-1914-3p*	Lung cancer	Jin et al. (2020a)
ALKBH5↓	Repression of autophagy, metastasis	*UBE2C*	Lung cancer	Guo et al. (2018)
ALKBH5	Anti-metastatic	*lncRNA GAS5-AS1*	Cervical cancer	Wang et al. (2019b)
ALKBH5	Metastasis	*Rp11*	CRC	Wu et al. (2019)

↓Indicates downregulated expression and ↑indicates upregulated expression in cancer. *HCC* is hepatocellular carcinoma, *CRC* is colorectal carcinoma and *GC* is gastric cancer

METTL3/*miR-143-3p*/*VASH1*/*VEGFA*, METTL3-YTHDF1/3-eIF3b/*YAP*, METTL3/*MALAT1*/*miR-1914-3p*/*YAP*, YTHDF2/*AXIN1*/Wnt/β-catenin, ALKBH5-YTHDF2/*YAP*, ALKBH5-HuR/*miR-1914-3p*/*LAST2*/YAP, FTO-E2F1/*NELL2*, and ALKBH5/*UBE2C* (Guo et al. 2018; Jin et al. 2019a; Jin et al. 2020a; Li et al. 2021b; Wang et al. 2019a; Wang et al. 2021c). In breast cancer, YTHDF3-induced translation of m^{6}A-enriched transcripts for *ST6GALNAC5*, *GJA1* and *EGFR* promotes brain metastasis (Chang et al. 2020).

The above-mentioned m^{6}A-mediated liver-, lung- and brain-specific metastasis in various cancers are summarized in Fig. 3. Whether m^{6}A modification and related regulators could serve as biomarkers and targets for cancer metastasis organotropism still warrants extensive studies.

The Clinical Translational Potential of the m^{6}A Axis in Cancer Diagnosis and Treatment

Given the essential functions of the m^{6}A axis in cancer development, the clinical translation potential of m^{6}A has attracted increasing attention. The m^{6}A axis has become a promising target for diagnosis, prognostic prediction and therapy.

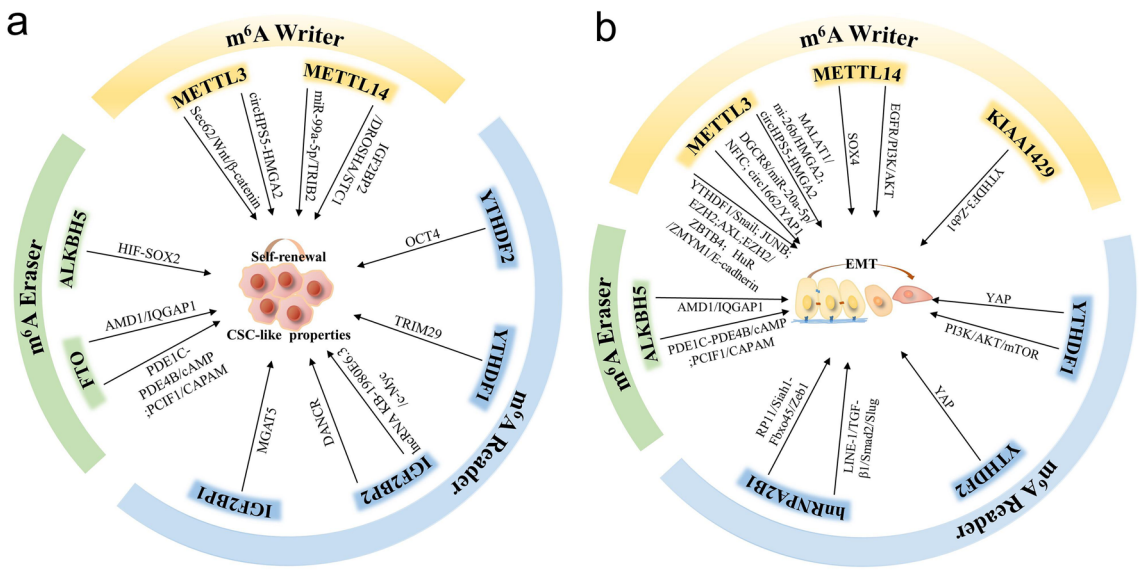


Fig.2 The functions of m^{6}A regulators in maintaining CSC-like properties and inducing EMT. The schematic diagrams showed the shared common functions of m^{6}A-mediated CSC-like features and EMT in **a** and **b**, respectively. The m^{6}A regulators, including writers, readers and erasers, have been extensively studied how to affect CSC and EMT, which are two critical biological events to drive cancer metastasis

Ge et al. claimed that m^{6}A modification has the potential to serve as an ideal biomarker in GC progression (Ge et al. 2020). It was reported that the m^{6}A levels are significantly increased in the peripheral blood RNA in GC, compared to benign gastric disease (BGD) and healthy controls (HCs). Furthermore, m^{6}A levels exhibit an elevated trend with the progression and metastasis of GC (Ge et al. 2020).

Our group comprehensively assessed the clinically predictive potential of m^{6}A modification, HCC progression and therapeutic responses. According to the established m^{6}A score system, three distinct m^{6}A patterns were identified in HCC. The HCC cluster with a lower m^{6}A score frequently showed metabolic hyperactivity, better prognosis and lower response rate to sorafenib treatment. In contrast, the HCC cluster with a higher m^{6}A score usually exhibited hypoactive metabolism, poorer prognosis, and favorable response to sorafenib therapy (Shen et al. 2020). In future, these findings still need to be confirmed in a large cohort, and further efforts are required to explore the clinical translation potential of the m^{6}A machinery in HCC metastasis.

Recently, targeting the critical enzymes of m^{6}A modification for cancer therapy has made some inspiring progressions. For example, METTL3 contains a Rossmann fold, which binds the S-adenosyl methionine (SAM) methyl donor. STM2457 is a bioavailable inhibitor of METTL3 catalytic activity through a SAM-competitive mode, which has been developed to apply for the treatment of acute myeloid leukemia (AML) (Yankova et al. 2021). For m^{6}A demethylases, two targeted FTO inhibitors, FB23 and FB23-2, have also been designed. FB23-2 significantly inhibits the progression of AML in cell lines and xeno-transplanted mice (Huang et al. 2019). Moreover, the two potent inhibitors of FTO showed promising anti-tumor effects in multiple types of cancers (Su et al. 2020). Another FTO-targeted molecule, Saikosaponin D (SsD), increases the global m^{6}A RNA methylation, effectively overcoming FTO/m^{6}A-mediated resistance to tyrosine kinase inhibitors in leukemia (Sun et al. 2021).

In view of the widespread clinical application of chemotherapy and targeted therapies in metastasis treatment, researchers have also explored the possibility of co-administration of m^{6}A-related molecules. Depletion of methyltransferases, METTL3 and METTL14, was found to enhance the response to anti-PD-1 treatment in CRC and melanoma, by increasing cytotoxic tumor-infiltrating CD8 + T cells and elevating the secretion of IFN-γ, CXCL9, and CXCL10 in the tumor microenvironment (Wang et al. 2020a; Yang et al. 2019). Similarly, the deletion of the m^{6}A demethylase ALKBH5 modulates the composition of tumor-infiltrating Treg and myeloid-derived suppressor cells, thereby sensitizing tumors to cancer immunotherapy (Li et al. 2020b). Despite the promising perspective of m^{6}A in clinical translation, we should be aware that most of the results were achieved in vitro or

in mice models. Large-scale clinical trials are urgently required to evaluate the effectiveness of targeting m^{6}A for cancer therapy.

Nowadays, with the development of m^{6}A mapping technologies, such as Mazter-Seq, it is possible to determine the precise quantity of m^{6}A modification at specific sites of specific RNAs (Garcia-Campos et al. 2019). These new methods will greatly promote the clinical application of m^{6}A as a novel biomarker. Additionally, the combination of m^{6}A and target therapy or immune therapy may be a promising strategy for anti-metastasis treatment.

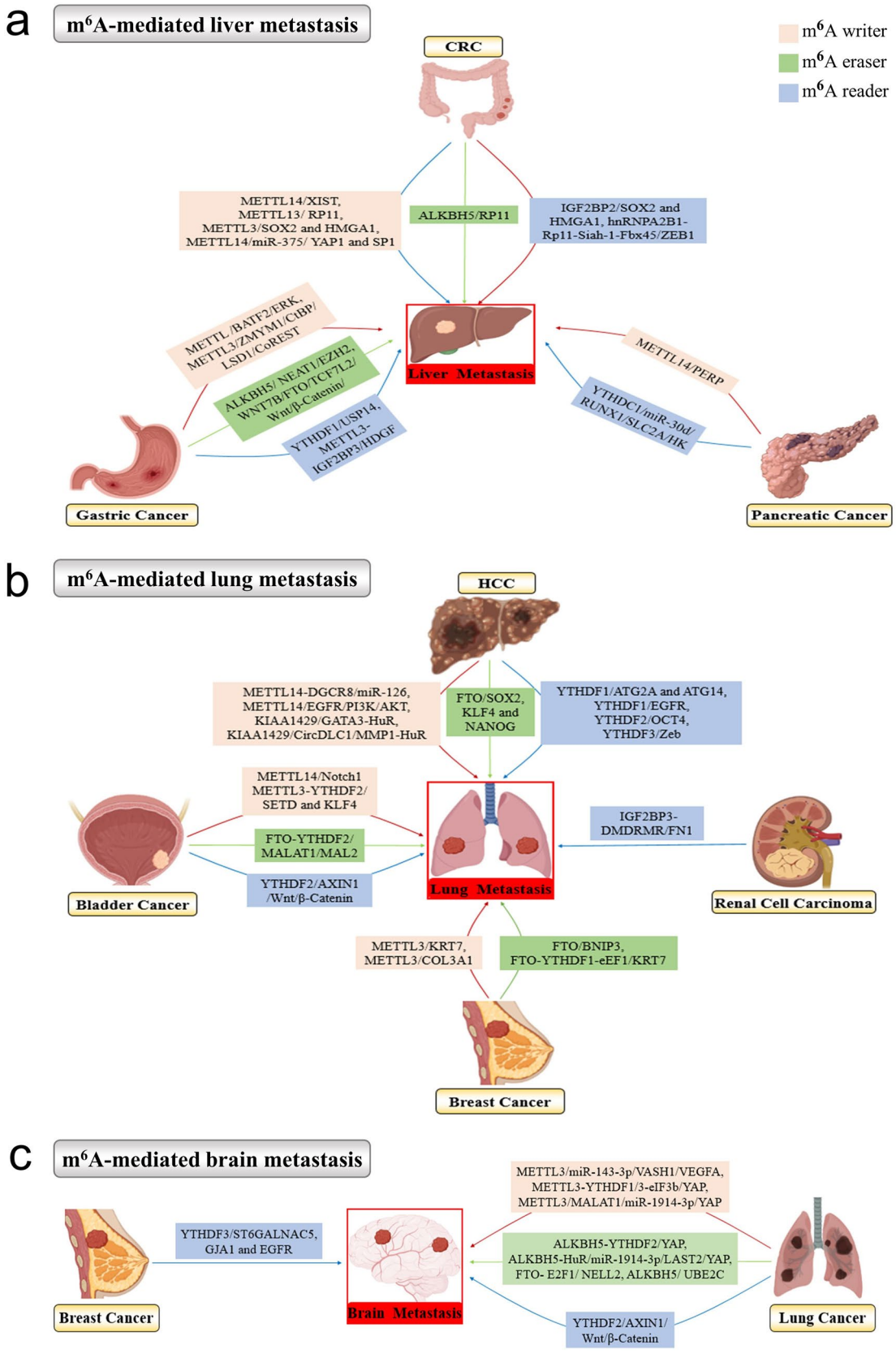
Limitations and Future Perspectives of m^{6}A Modifications

Despite the great progression of m^{6}A-related research in cancer development, there are still some limitations to be noted. First, the writers, readers and erasers of m^{6}A are not specific to a single target, and m^{6}A regulators have multiple substrates, including oncogenes and tumor suppressor genes. These may explain the controversial roles of a single m^{6}A regulator that may exert opposite functions. Meanwhile, the uncertainty of m^{6}A-targeting also increases the difficulty to develop a therapeutic strategy. Second, m^{6}A modification may induce completely different effects on RNA metabolism. For some RNAs, m^{6}A enrichment may facilitate RNA decay, such as *EGFR*, *Oct4* and *Sox2*, but in some cases, m^{6}A deposition may increase the stability of the RNA, such as in the case of tumor suppressor *KLF14*. The different fates of m^{6}A-RNAs may develop in a contextspecific manner for different targets and different types of cancers, and the underlying mechanisms need to be clarified. Additionally, a single m^{6}A regulator may display different expression patterns in different cancers, as well as in the same type of cancer. Taking METTL14 as an example, it is downregulated in multiple types of cancers and can inhibit cancer metastasis, but in pancreatic cancer, METTL14 is upregulated, promoting metastasis (Wang et al. 2020b). Another example is METTL3, several studies have demonstrated that METTL3 is upregulated and acts as an oncogene in breast cancer (Chen et al. 2021b; Xie et al. 2021). However, Shi et al. reported that METTL3 is downregulated and can inhibit the development of breast cancer (Shi et al. 2020a). These inconsistencies may result from different pathogenesis pathways and backgrounds of different cancer types. Moreover, the heterogeneity of cancer may lead to a discrepancy.

The m^{6}A modification is a new frontier in the cancer field, and most of the present studies focus on it in cancer cells. As the microenvironment is essential for cancer metastasis, further study of m^{6}A alterations and functions in the tumor microenvironment are warranted. Additionally, it is important to identify the determinative m^{6}A site with a regulatory function, as some m^{6}A sites may present just a constitutive event lacking of function. A particular m^{6}A signature in some specific transcript loci may be more informative than the global m^{6}A profiles, which would serve as better biomarkers for clinical translation in cancer. These promising perspectives of m^{6}A deserve to be further probed in future investigations.

Conclusion

Cancer metastasis is a complicated biological event and accounts for a high mortality rate. The m^{6}A modifications may exert versatile roles to determine the fate of RNAs, which play essential roles in regulating cancer development. Through systematically reviewing the latest progression of m^{6}A modification in cancer metastasis, we hope to comprehensively enrich our knowledge on m^{6}A regulation


a
m6A-mediated liver metastasis
m6A writer
m6A eraser
m6A reader
CRC
METTL14/XIST, METTL13/ RP11, METTL3/SOX2 and HMGA1, METTL14/miR-375/ YAP1 and SP1
ALKBH5/RP11
IGF2BP2/SOX2 and HMGA1, hnRNPA2B1-Rp11-Siah-1-Fbx45/ZEB1
METTL /BATF2/ERK, METTL3/ZMYM1/CtBP/ LSD1/CoREST
ALKBH5/ NEAT1/EZH2, WNT7B/FTO/TCF7L2/ Wnt/β-Catenin/
YTHDF1/USP14, METTL3-IGF2BP3/HDGF
Liver Metastasis
METTL14/PERP
YTHDC1/miR-30d/ RUNX1/SLC2A/HK
Gastric Cancer
Pancreatic Cancer
b
m6A-mediated lung metastasis
HCC
METTL14-DGCR8/miR-126, METTL14/EGFR/PI3K/AKT, KIAA1429/GATA3-HuR, KIAA1429/CircDLC1/MMP1-HuR
FTO/SOX2, KLF4 and NANOG
YTHDF1/ATG2A and ATG14, YTHDF1/EGFR, YTHDF2/OCT4, YTHDF3/Zeb
METTL14/Notch1 METTL3-YTHDF2/ SETD and KLF4
FTO-YTHDF2/ MALAT1/MAL2
YTHDF2/AXIN1 /Wnt/β-Catenin
Lung Metastasis
IGF2BP3-DMDRMR/FN1
Bladder Cancer
Renal Cell Carcinoma
METTL3/KRT7, METTL3/COL3A1
FTO/BNIP3, FTO-YTHDF1-eEF1/KRT7
Breast Cancer
c
m6A-mediated brain metastasis
METTL3/miR-143-3p/VASH1/VEGFA, METTL3-YTHDF1/3-eIF3b/YAP, METTL3/MALAT1/miR-1914-3p/YAP
YTHDF3/ST6GALNAC5, GJA1 and EGFR
ALKBH5-YTHDF2/YAP, ALKBH5-HuR/miR-1914-3p/LAST2/YAP, FTO- E2F1/ NELL2, ALKBH5/ UBE2C
YTHDF2/AXIN1/ Wnt/β-Catenin
Breast Cancer
Brain Metastasis
Lung Cancer

◂**Fig.3** The m^{6}A-mediated organ-specific metastasis in various cancers. The schematic diagram indicated the m^{6}A-mediated liver metastasis (**a**), lung metastasis (**b**), and brain metastasis (**c**) in different cancers, and the m^{6}A writers, readers and erasers all play essential roles in the organ-specific metastatic process. The diagram of various cancer types were created with the help of BioRender.com

and provide some new clues to develop effective strategies to monitor and treat cancer metastasis based on m^{6}A dysregulation.

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Declarations

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Ethical Approval Not applicable.

Consent to Participate Not applicable.

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