Mechanisms of N6-methyladenosine modification in tumor development and potential therapeutic strategies (Review)

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Abstract. N6-methyladenosine (m6A) modification, as the most common and abundant type of RNA modification in mammalian cells, participates in the processes of mRNA transcription, translation, splicing and degradation, serving to regulate RNA stability. In recent years, a large number of studies have indicated that m6A modification is able to affect tumor progression, participate in tumor metabolism, regulate tumor cell ferroptosis and change the tumor immune microenvironment, thereby affecting tumor immunotherapy. In the current review, the main features of m6A-associated proteins are presented with a focus on the mechanisms underpinning their roles in tumor progression, metabolism, ferroptosis and immunotherapy, also emphasizing the potential of targeting m6A-associated proteins as a promising strategy for the treatment of cancer.

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Abbreviations: m6A, N6-methyladenosine; UTR, untranslated region; MTC, methyltransferase complex; SAM, S-adenosylmethionine; METTL3, methyltransferase-like 3; RBM15, RNA-binding motif protein 15; WTAP, Wilms tumor 1-associated protein WTAP; ZC3H13, zinc finger CCCH domain-containing protein 13; U6 snRNA, U6 small nuclear RNA; FTO, fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate-dependent dioxygenase homolog 5; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; eIF3, eukaryotic initiation factor 3; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; XIST, X inactivation-specific transcript; 80S TIC, 80S translation initiation complex; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HOXA10, homeobox A10; BCSC, breast cancer stem cell; WIF-1, Wnt inhibitory factor 1; PER1, period circadian regulator 1; LXRA, liver X receiver α; HIVEP2, human immunodeficiency virus type I enhancer binding protein 2; CYLD, cyclindromatosis; YAP, Yes-associated protein; EMT, epithelial mesenchymal transition; PDK4, pyruvate dehydrogenase kinase 4; GLUT1, glucose transporter protein 1; HK2, hexokinase 2; GLUT4, glucose transporter 4; ENO2, enolase 2; BPTF, bromodomain PHD finger transcription factor; SRC, SRC proto-oncogene nonreceptor tyrosine kinase; APOE, apolipoprotein E; CK2, casein kinase 2; ATF4, activating transcription factor 4; GLS1, glutaminase-1; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Siah2, seven in absentia homolog 2; ICP, immune checkpoint; AML, acute myeloid leukemia; GBM, glioblastoma multiforme; OvCa, ovarian cancer

Contents

1. Introduction

N6-methyladenosine (m6A), discovered in the 1970s, is a type of methylation modification that occurs on the sixth nitrogen atom of adenosine, which is the major form of mammalian mRNA methylation (1). In mammalian cells, each mRNA molecule contains three m6A residues on average and m6A is mostly enriched around the stop codon, near the long internal exon, and in the 3'-untranslated region (3'-UTR), which is involved in almost all steps of RNA metabolism (2-4).

Key words: N6-methyladenosine, cancer, metabolism, ferroptosis, treatment

The increased proliferative capability of tumor cells and their enhanced ability of invasive migration may lead to an increase in tumor malignancy, which affects the prognosis of patients. Tumor metabolic reprogramming, as one of the important tumor markers, provides energy supply for tumor growth and fulfills an important role in tumor progression (5). Ferroptosis, an intracellular iron-dependent form of regulated cell death that is distinct from apoptosis, necrosis and autophagy, also affects tumor progression. Recent studies have revealed that m6A-associated factors are able to alter the proliferative, invasive and migratory capabilities of tumor cells, regulate tumor metabolism and participate in the process of ferroptosis in tumors, thereby affecting tumor progression (6-9). Furthermore, m6A-associated factors have been shown to alter the tumor immune microenvironment, providing novel insight into, and strategies for, the immunotherapy of tumors, and inhibitors of m6A-associated proteins are also anticipated to potentially serve as novel and promising anti-cancer agents in the future treatment of cancer.

Given the important role of m6A in cancer research, collating and summarizing new research findings on the role of m6A in cancer, and presenting these latest findings and developmental trends, are essential for researchers to gain a deeper understanding of the latest developments on m6A in cancer research. However, the present crop of reviews that have been published on the role of m6A in cancer may broadly be divided into two major categories: One that summarizes the mechanism of action of m6A in only one type of cancer, and the other that, although summarizing the mechanism of action of m6A in multiple types of cancer, either focuses on the effects of m6A on tumor progression or on its effects on tumor metabolism.

The present review first provided a comprehensive summary of the mechanisms associated with m6A modification in various types of cancer (i.e., tumor progression and tumor metabolism), highlighting the importance of m6A in regulating tumor metabolism and influencing tumor progression. Furthermore, the association between m6A and ferroptosis, another current hot topic in this area of research, was explored. Finally, the important roles of m6A in immunotherapy and clinical targeted therapy were emphasized, with the aim of showing how targeting m6A is expected to bring new hope for cancer treatment.

2. m6A modifications

m6A modifications have been indicated to have participatory roles in tumor metabolism, tumor immune regulation and ferroptosis, and the entire process comprises a series of proteins that are classified into three categories, namely methyltransferases, demethylases and m6A recognition binding proteins, also known as writers, erasers and readers, respectively (10) (Fig. 1).

m6A writers/methyltransferases. The installation of m6A on mRNA or non-coding RNA may be catalyzed by a methyltransferase complex composed of several proteins, and these enzymes that are able to catalyze the transfer of a methyl group from S-adenosylmethionine (SAM) to the N-6 position of adenosine are called methyltransferases, also known as 'writers' (11). In 1994, Bokar *et al* (12) purified methyltransferase into a protein complex for the first time, thereby identifying it as a multi-component complex. To date, the following methyltransferases have been identified: Methyltransferase-like 3 (METTL3), METTL14, RNA-binding motif protein 15 (RBM15)/RBM15B, Wilms tumor 1-associated protein (WTAP), Vir like M6A methyltransferase associated (VIRMA)/KIAA1429, the E3 ubiquitin-protein ligase Hakai (HAKAI), zinc finger CCCH domain-containing protein 13 (ZC3H13) and METTL16.

METTL3 promotes the translation of human oncogenes and drives the progression of many types of tumors (including lung cancer, gastric cancer and pancreatic cancer) (13-15). METTL14 can not only catalyze the methylation of m6A RNA, but it also forms a stable METTL3-METTL14 heterodimer complex with METTL3 and participates in the methylation modification of mammalian m6A through mediating the deposition of m6A on mammalian cell nuclear RNA (16). The METTL3-METTL14 heterodimer complex fulfills a crucial role in the m6A methylation modification process. The METTL3-METTL14 heterodimer is able to interact with WTAP without methylation activity, thereby affecting the deposition of m6A (16). It may also be directed towards specific targets and modify m6A with the assistance of RBM15/RBM15B without catalytic function (17), and can also be recruited by VIRMA/KIAA1429 to guide the process of methylation modification (18).

In addition, WTAP, as the regulatory subunit of m6A methyltransferase, has been shown to be involved in regulating the recruitment of m6A methyltransferase complex to specific mRNA targets, thereby affecting the activity of methyltransferase in mammals (19).

The methyltransferase HAKAI is also an E3 ubiquitin ligase that promotes the process of epithelial-mesenchymal transition (EMT) in tumors through mediating downregulation of the expression levels of E-cadherin, which is essential to maintain the stability of m6A mRNA (20). The zinc finger protein ZC3H13 is also a key methyltransferase, which assists in the anchorage of WTAP, Virilizer (KIAA1429 human homologous protein) and HAKAI in the nucleus to promote the process of m6A methylation; thereby, ZC3H13 has an important role in regulating RNA m6A methylation in the nucleus (21). METTL16 is a conserved U6 small nuclear RNA (U6 snRNA) methyltransferase that adds m6A tags on to U6 snRNA and SAM synthase precursor mRNA, and is able to regulate methyl donor SAM homeostasis through activating methionine adenosyltransferase 2A splicing and regulating SAM synthase (22,23).

m6A erasers/demethylases. m6A demethylase is an enzyme that is able to directly remove the m6A modification from mRNA, hence the name 'eraser'. In 2011, Jia *et al* (24) discovered the first demethylase, which also functions as an obesity genetic factor, namely fat mass and obesity-associated protein (FTO), which was shown to have oxidative demethylation activity through a series of *in vitro* experiments, effectively reversing the m6A modification on mRNA via oxidation and demethylation (24). Although FTO was initially considered to be associated with weight gain and obesity, more recent studies have focused on its role in tumor formation and progression.

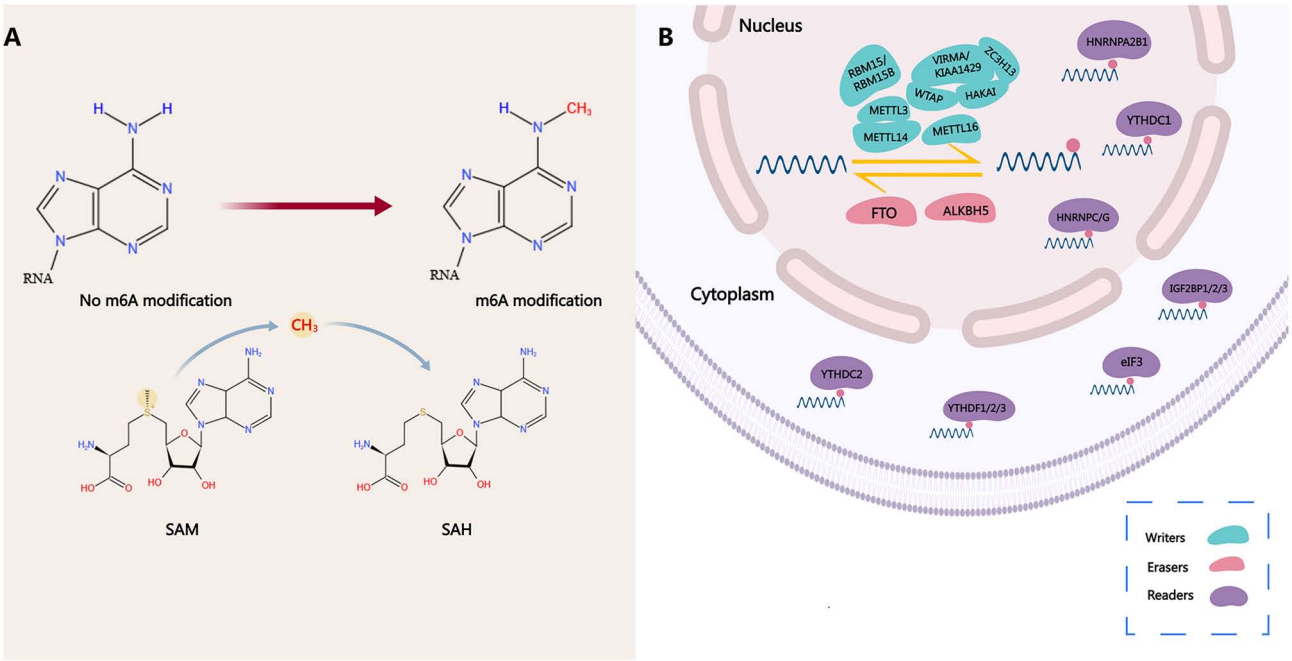

Figure 1. Process of m6A modification. (A) SAM is a methyl donor for almost all eukaryotic cell methylation reactions and it maintains RNA methylation through the activity of RNA methyltransferase. Methyltransferases catalyze the transfer of a methyl group from SAM to the N-6 position of adenosine. At the same time, after demethylation, SAM is converted into SAH. (B) m6A modification is a dynamic and reversible process. The modification of m6A is catalyzed by a methyltransferase complex consisting of METTL3 and METTL14 and its cofactors WTAP, RBM15/RBM15B, VIRMA/KIAA1429, ZC3H13, HAKAI and METTL16 ('writers'), wherein METTL3 and METTL4 constitute the catalytic subunit m6A-METTL complex, and WTAP, VIRMA/KIAA1429, ZC3H13 and HAKAI constitute the regulatory subunit m6A-METTL-associated complex. The m6A modification can be removed by the demethylating enzymes FTO and ALKBH5 ('erasers'). m6A functions by recruiting m6A binding proteins ('readers') such as YTHDF1/2/3, YTHDC1/2, IGF2BP1/2/3, HNRNPA2B1 and HNRNPC/G, which participate in mRNA transcription, translation, splicing and degradation processes, thereby regulating their stability. YTHDC1 is associated with RNA splicing and RNA nuclear output in the nucleus; HNRNPA2B1 and HNRNPC/G are associated with RNA splicing and miRNA processing in the nucleus; IGF2BP1/2/3 is associated with RNA stability; YTHDC2, YTHDF1/3 and eIF3 are associated with RNA translation in the cytoplasm; and YTHDF2/3 is associated with RNA attenuation in the cytoplasm. SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; m6A, N6-methyladenosine; METTL3/4, methyltransferase-like 3/4; WTAP, Wilms tumor 1-associated protein; FTO, fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate-dependent dioxygenase homolog 5; IGF2BP1/2/3, IGF2 binding protein 1/2/3; YTHDF1/2/3, YTH domain family protein 1/2/3; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; eIF3, eukaryotic initiation factor 3; RBM15/RBM15B, RNA-binding motif protein 15/RNA-binding motif protein 15B; VIRMA, Vir like M6A methyltransferase associated; HAKAI, E3 ubiquitin-protein ligase Hakai; ZC3H13, zinc finger CCCH domain-containing protein 13.

Soon after, in 2013 Zheng *et al* (25) identified a second demethylase, α-ketoglutarate-dependent dioxygenase homolog 5 (ALKBH5), which was shown to affect mRNA export and RNA metabolism through the oxidative demethylation of abundant m6A residues on mRNA. FTO has been shown to be localized in the nucleus and cytoplasm, whereas ALKBH5 is localized in the nucleus and co-localizes with nuclear spots; therefore, both FTO and ALKBH5 are able to exert an effect on the splicing of mRNA (25,26). The last m6A demethylase to be discussed herein is ALKBH3, although its substrates are predominantly transfer RNAs (27). Taken together, the various reports published on demethylases to date have suggested that their presence dictates that m6A RNA methylation modification is a reversible process that can be dynamically regulated.

m6A readers/m6A-binding proteins. m6A-binding proteins, also known as 'readers', are a class of proteins that are able to recognize and bind to m6A-modified RNA, and yield specific phenotypic results through regulating a variety of processes. Dominissini *et al* (3) demonstrated that proteins containing YTH domains were m6A-binding proteins, including YTH domain family protein 1/2/3 (YTHDF1/2/3) and YTH domain 1/2 (YTHDC1/2).

In addition, insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs, including the family members IGF2BP1/2/3) also belong to the m6A-binding protein family, which have been indicated to support the malignant state of cancer cells by promoting the stability of mRNA and/or increasing its storage (28).

Eukaryotic initiation factor 3 (eIF3), which fulfills a core role in mammalian cell translation initiation, has also been identified as an m6A-binding protein. Heterogeneous nuclear ribonucleoprotein A2B1 (HNRNPA2B1) binds directly to m6A sites in the transcriptome, and considering that it regulates the variable splicing of exons in a set of transcripts, it is therefore identified as an m6A-tagged nuclear reader and effector (29).

3. Targeting m6A in tumor growth and metastasis

Numerous studies have confirmed that METTL3 is able to promote the proliferation of tumor cells, increase the incidence of tumor metastasis and have a significant positive role in tumor progression. METTL3 may participate in all stages of the RNA life cycle via regulating m6A modifications in mRNA; it has been shown to promote the growth and invasion of bladder cancer cells through the ALF

transcription elongation factor 4/NF-κB/MYC signaling pathway in an m6A-dependent manner, and it has also been shown to promote the progression of bladder cancer by regulating non-coding RNA, i.e., it promotes the maturation of pri-microRNA (miR)221/222, thereby enhancing the proliferation of bladder cancer cells (30,31). In addition, the 'writer' methyltransferase METTL3 is able to combine with the 'reader' IGF2BP2 to maintain the expression of sex-determining region Y (SRY)-box 2 (SOX2) in colorectal cancer cells in an m6A-dependent manner, thereby exerting a pro-cancer effect through their working together (32). METTL3 also exerts an active role in gastric cancer. METTL3 stabilizes and enhances the mRNA expression of zinc finger MYM-type containing 1 (ZMYM1) through an m6A-HuR-dependent pathway, which leads to the binding of ZMYM1 to the C-terminal binding protein/lysine-specific demethylase 1/corepressor of RE1 silencing transcription factor complex, thereby targeting and repressing E-cadherin transcription, leading to an increase in EMT and promoting the metastasis of gastric cancer cells (33).

METTL14 is an N6-adenosine methyltransferase that is able to affect tumor growth through regulating the function of RNA. In certain cases, the 'writer' METTL14 has been demonstrated to promote tumor progression in an m6A-dependent manner. In pancreatic cancer, overexpression of METTL14 can directly act on the downstream target p53 apoptosis effector related to PMP22 (PERP; a p53 target gene) through m6A modification, leading to a decrease in PERP levels and a marked enhancement of the growth and metastasis of pancreatic cancer cells (34). However, in most cases, METTL14 is involved in tumor biological processes as a tumor suppressor. It was shown that knockdown of METTL14 in colorectal cancer leads to reduced m6A-methylation levels of X inactivation-specific transcript (XIST), a newly identified long non-coding RNA (lncRNA), and enhanced XIST expression, resulting in the enhanced proliferation and invasion of colorectal cancer cells (35). Furthermore, METTL14 was also found to inhibit the metastasis of colorectal cancer through mediating the m6A modification of SRY-related high-mobility-group box 4 (SOX4) mRNA (36). In addition, METTL14-mediated degradation of both XIST and SOX4 mRNA was shown to be dependent on the YTHDF2-dependent pathway of the m6A reader protein (35,36). METTL14 may also inhibit the growth and metastasis of gastric cancer via stabilizing the expression of phosphatase and tensin homologue mRNA or inactivating the PI3K/AKT/mTOR pathway and the EMT (37,38).

It should be noted that ZC3H13 and METTL14 are similar: Both proteins may function as tumor suppressor genes to mediate the tumor immune response and fulfill a role in promoting immunosuppression in breast cancer cells (39). WTAP, an oncogenic protein, has been shown to promote the progression of hepatocellular carcinoma through mediating m6A modification to silence ETS proto-oncogene 1 (40).

KIAA1429, a scaffold protein that functions as a catalytic core component of the bridging m6A methyltransferase complex, also promotes the progression of hepatocellular carcinoma by inducing m6A methylation at the 3'-UTR of the pre-mRNA of the oncogene GATA binding protein 3 (GATA3), leading to the degradation of GATA3 pre-mRNA and thereby promoting tumor invasion and metastasis (18). In addition, the expression levels of KIAA1429 and its m6A were found to be abnormally high in lung adenocarcinoma, thereby regulating the expression of mucin 3A in an m6A-modified manner and promoting the proliferation, invasion and migration of lung adenocarcinoma cells (41).

METTL16 has also been shown to serve a non-methylation-dependent role in promoting the formation of the 80S translation initiation complex through the interaction of its methyltransferase structural domain with eIF3a/b and ribosomal RNA, thereby promoting the growth, migration and invasion of hepatocellular carcinoma cells (42).

As the first identified demethylase, FTO was shown to act as a positive regulator of the progression and metastasis of a variety of different types of tumor. In HER2-positive breast cancer cells, FTO was found to accelerate tumor migration and invasion through the FTO/miR-181b-3p/ADP ribosylation factor like GTPase 5B signaling pathway (43). As an oncogene, FTO has been shown to be associated with the prognosis of bladder cancer and it regulates the methylation of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) to promote tumor cell growth; subsequently, MALAT1 interacts with miR-384 to further regulate MAL2 expression, thereby promoting the progression of bladder cancer (44). During metastasis, the expression level of FTO is abnormally increased in endometrial cancer tissues, thereby promoting the expression of homeobox (HOX)B13, which activates the WNT signaling pathway, further enhancing endometrial cancer metastasis by removing the methylation modification of the 3'-UTR region of HOXB13 mRNA and eliminating the recognition of this region by YTHDF2 (45).

ALKBH5, another m6A demethylase, has been shown to promote the progression of multiple types of solid tumors and to promote the self-renewal of cancer stem cells (46). In epithelial ovarian cancer, ALKBH5 has been shown to mediate the m6A demethylation of Janus kinase 2 (JAK2) mRNA, leading to the inhibition of YTHDF2-mediated mRNA degradation and the maintenance of JAK2 mRNA expression; furthermore, ALKBH5 joins with its upstream transcription factor, HOXA10, in a regulatory loop to maintain ALKBH5 and HOXA10 overexpression in tumors, thereby activating the JAK2/STAT3 signaling pathway to promote tumor growth (47). In addition, ALKBH5 has been shown to enhance both the stability of Bcl-2 mRNA and the interaction between Bcl-2 and Beclin1, a key protein in autophagy, through catalyzing m6A demethylation, which subsequently promoted the proliferation and migration of ovarian cancer cells (48). When breast cancer cells are exposed to hypoxic conditions, ALKBH5 expression has been shown to be promoted in a hypoxia-inducible factor-dependent manner. Overexpressed ALKBH5 may enhance the stability of NANOG mRNA, thereby increasing its expression level and inducing an increase in the breast cancer stem cell phenotype via mediating m6A demethylation, which leads to the promotion of breast cancer progression (49). Overexpression of ALKBH5 in gastric cancer has been shown to induce the demethylation of nuclear paraspeckle assembly transcript 1, leading to an upregulation of its expression level, which induces upregulation of the expression of EZH2, ultimately leading to the enhancement of invasion and metastasis of gastric cancer cells (50). However,

it is notable that numerous studies have demonstrated that ALKBH5 also has a role in inhibiting tumor progression. In pancreatic cancer cells, overexpression of ALKBH5 has been shown to interfere with Wnt signaling through inhibiting the m6A modification of Wnt inhibitory factor 1, which leads to an attenuation of the ability of pancreatic cancer cells to proliferate and migrate, and also enhances their sensitivity to chemotherapeutic agents (51). A subsequent study revealed that inhibition of ALKBH5 expression in pancreatic cancer leads to downregulation of the mRNA level of the tumor suppressor period circadian regulator 1 in an m6A-YTHDF2-dependent manner, a process that promotes the progression of pancreatic cancer (52). Therefore, several studies have demonstrated how ALKBH5 fulfills a dual role in regulating tumor progression; that is, it may exert different roles in different types of tumor by regulating various biological processes.

m6A readers likewise influence tumor progression. The YTH structural domain family, including YTHDF1/2/3, is able to preferentially recognize m6A-modified mRNAs, thereby exerting an important role in tumor progression.

YTHDF1 has been shown to promote the growth and metastasis of ovarian cancer cells and to fulfill a key oncogenic role in ovarian cancer, in which the underlying mechanism may be that YTHDF1 regulates the protein expression of its downstream target, eIF3c, and its translation in an m6A-dependent manner, which, in turn, affects the progression of ovarian cancer (53).

In addition, it was found that YTHDF2 exerts a key role in the m6A-dependent regulatory mechanism of glioblastoma, and it may be involved in the malignant progression of glioblastoma through multiple pathways. On the one hand, YTHDF2 may promote glioblastoma growth via stabilizing MYC and VEGFA transcription and targeting IGF2BP3 through m6A RNA modification (54); on the other hand, the protein expression level of YTHDF2 is regulated by the EGFR/SRC/ERK signaling pathway in glioblastoma, and its regulation of liver X receiver α and HIV type I enhancer binding protein 2 occurs in an m6A-dependent manner, ultimately promoting the proliferation and invasion of tumor cells (55). Overexpression of YTHDF2 promotes the growth and metastasis of prostate cancer cells, probably since YTHDF2 both promotes the mRNA degradation of the tumor suppressors phospholysine phosphohistidine inorganic pyrophosphate phosphatase and NK3 homeobox 1, and regulates AKT phosphorylation to promote prostate cancer progression (56). The expression level of YTHDF2 has also been shown to be associated with the prognosis of patients with hepatocellular carcinoma, and it both promotes the hepatocellular carcinoma stem cell phenotype and enhances tumor metastasis through increasing the level of m6A in the 5'-UTR of OCT4 mRNA (57). However, it is noteworthy that YTHDF2 is also able to act as a tumor suppressor in certain cases. It was found that overexpressed YTHDF2 was able to inhibit the growth and proliferation of hepatocellular carcinoma cells and induce apoptosis via promoting the degradation of EGFR mRNA, thereby hindering the progression of stem cell carcinoma (58). Accordingly, YTHDF2 fulfills different roles in different tumors.

The expression level of YTHDF3 has been shown to be associated with the development of brain metastases from breast cancer. It was found that overexpression of YTHDF3 both led to an increase in the binding of eIF3a to ST6GALNAC5, GJA1 and EGFR, and promoted the translation of these transcripts, thereby exerting a key role in the process of breast cancer brain metastasis (59). In colorectal cancer, growth arrest-specific 5 (GAS5) has been shown to inhibit the growth of colorectal cancer cells by phosphorylating Yes-associated protein (YAP) to induce its ubiquitination and degradation, whereas YTHDF3 is able to reverse the tumor suppression effects via binding to m6A-modified GAS5 and degrading GAS5, thereby leading to the progression of colorectal cancer (60).

The role of 'reader' YTHDC1 on RNA splicing is of great value in tumor progression (61). In lung cancer, nuclear Aurora kinase A was found to induce YTHDC1 to splice the tumor suppressor RNA-binding protein 4 in an abnormal manner, which provides a novel target for the target-directed treatment of lung cancer (62).

In general, YTHDC2 acts as a tumor suppressor gene with low expression in tumor tissues, including non-small cell lung cancer and head and neck squamous cell carcinoma (63,64). In lung cancer tissue, YTHDC2 has a role in maintaining the stability of tumor suppressor cyclindromatosis through m6A modification, such that the downregulation of YTHDC2 promotes the proliferation and invasion of lung cancer cells (65).

IGF2BPs are upregulated in most tumors and are associated with tumor growth (66). IGF2BP1 has been shown to enhance the expression of serum response factor through binding to a conserved 3'-UTR and acting in an m6A-dependent manner, thereby enhancing the invasive phenotype of tumors (67). In addition, IGF2BP1 has been shown to exert a positive role in the progression of endometrial cancer. IGF2BP1 and the mRNA stabilizer polyadenylate-binding protein 1 are able to jointly maintain the stability of paternally expressed 10 mRNA and promote its expression, thereby accelerating the proliferation of endometrial cancer cells (68). Therefore, IGF2BP1 may be a potential target for the treatment of endometrial cancer.

Considering IGF2BP2, this protein is typically involved in regulating the stability of mRNA, exerting a positive role in tumor cell proliferation, invasion and metastasis. IGF2BP2 acts as an m6A reader that is able to identify the m6A methylation of the lncRNA differentiation antagonizing non-protein coding RNA, thereby delaying its mRNA degradation, increasing its stability and promoting its expression, which ultimately achieves the goal of promoting the stem cell characteristics of pancreatic cancer and accelerating the growth of pancreatic cancer (69). In colorectal cancer, IGF2BP2 also acts as a tumor promoter, recognizing YAP mRNA modifications and upregulating the expression of ErbB2 by increasing its stability, thereby promoting the proliferation, migration and invasion of colorectal cancer cells and inhibiting their apoptosis (70).

The expression level of IGF2BP2 was found to be associated with whether or not head and neck squamous cell carcinoma has lymph node metastasis. The mRNA of Slug, an EMT-associated protein, was found to be recognized and bound by IGF2BP2, an interaction that regulates Slug expression and maintains its mRNA stability, thereby promoting the lymphatic metastasis of head and neck squamous cell carcinoma cells (71).

The 'reader' IGF2BP3 also has an m6A reading role in colorectal cancer. It was demonstrated to promote tumor cell

proliferation and tumor angiogenesis via reading the m6A modifications of cyclin D1 and VEGF (72). A high expression level of IGF2BP3 in bladder cancer is frequently indicative of a poor prognosis and IGF2BP3 is able to enhance bladder cancer cell proliferation, promote cell cycle progression and inhibit apoptosis through activating the JAK/STAT pathway (73).

Of note, abnormal expression of circular RNAs (circRNAs) may affect m6A modifications (74). By interacting with IGF2BP1, the tumor suppressor circPTPRA was indicated to not only downregulate the expression of MYC and fascin actin-bundling protein 1, but also to impede the recognition of its downstream m6A-modified RNA by IGF2BP1, ultimately inhibiting the proliferation, migration and invasion of breast cancer cells (75). Similarly, overexpression of circNDUFB2 was observed to reduce the stability of IGF2BPs via the ubiquitin-proteasome pathway, leading to a significant inhibition of growth and metastasis in non-small cell lung cancer (76).

In general, m6A-associated enzymes have been shown to have a wide range of clinical significance in tumor growth and metastasis. Current research on the mechanism of m6A in tumor progression provides novel ideas and targets for the treatment of tumors. m6A-associated enzymes themselves are potential targets for a variety of tumor treatments, which should help patients to achieve a better prognosis (Table I).

4. Targeting m6A in tumor metabolism

When tumor cells face challenging conditions such as nutrient deficiency and hypoxia, they frequently carry out energy metabolism reprogramming to meet their own energy needs (77). The change of the energy metabolism mode is critically important for tumor occurrence, tumor cell growth and proliferation, and thus, metabolic reprogramming is regarded as a novel feature of tumors (78).

m6A and glucose metabolism. The Warburg effect, also known as aerobic glycolysis, as the name suggests, indicates that tumor cells preferentially undergo glycolysis even in the presence of oxygen, rather than providing energy for cell growth through the oxidative phosphorylation pathway. This metabolic approach gives tumor cells the ability to obtain energy through anaerobic glycolysis, providing the prerequisite energy for tumor cell proliferation and metastasis (79). Recent studies have confirmed that m6A-associated proteins are involved in the regulation of glycolysis in tumor cells (Fig. 2).

METTL3, as a tumor driver, promotes both the proliferative and invasive abilities of tumor cells, as well as cellular glycolysis, driving tumor progression. METTL3 is able to positively regulate the glycolysis of tumor cells through promoting the expression of pyruvate dehydrogenase kinase 4 (PDK4), and the stability of PDK4 mRNA is maintained by IGF2BP3, which exerts a positive role in promoting the growth of cervical cancer cells and liver cancer cells (80). METTL3, an important m6A-regulated enzyme in colorectal cancer cells, is also closely associated with glycolysis in colorectal cancer. It is able to mediate the downstream target glucose transporter protein 1 (GLUT1) through m6A modification, thereby regulating mechanistic target of rapamycin complex 1 (mTORC1) signaling, promoting glucose metabolism and increasing glucose uptake and lactate production (81). In addition, METTL3 has been shown to regulate the expression of hexokinase 2 (HK2) and GLUT1, and maintain both the level and stability of HK2 and GLUT1 mRNA, depending on its m6A methyltransferase activity and m6A reader IGF2BP2/3, thereby regulating glucose metabolism in colorectal cancer and promoting tumor progression (7). The expression level of METTL3 in gastric cancer cells may also be increased through inducing the activation of H3K27 acetylation. An increase in the expression level of METTL3 not only promotes the proliferation, metastasis and tumor vascular growth of gastric cancer cells, but also enhances the expression of glucose transporter 4 (GLUT4) and enolase 2 (ENO2) through the m6A modification of hepatoma-derived growth factor (HDGF) mRNA, thereby enhancing the glycolytic rate of gastric cancer cells and promoting tumor growth and liver metastasis (14). In cervical cancer, METTL3 also has a role in promoting glycolysis. The underlying mechanism may involve METTL3 regulating its downstream target HK2 and enhancement of the stability of HK2 in an m6A-dependent manner mediated by YTHDF1 (82).

The expression of METTL14 has been shown to be downregulated in renal cell carcinoma, particularly during the late metastatic stages. Since METTL14 is able to accelerate the degradation of bromodomain PHD finger transcription factor (BPTF) mRNA, a low expression level of METTL14 may activate ENO2 and SRC proto-oncogene nonreceptor tyrosine kinase (SRC) through an upregulation of the expression of BPTF, thereby promoting the occurrence of glycolysis and metastasis of renal cell carcinoma, and accelerating the progression of renal cell carcinoma (83).

WTAP fulfills the role of 'writer' in m6A modification, and is also able to influence the Warburg effect of cells and tumor progression. In breast cancer, C5aR1-positive neutrophils have been shown to induce WTAP phosphorylation at serine-341 through over-activating the ERK1/2 signal pathway to stabilize the expression of WTAP protein, thereby upregulating ENO1 expression and enhancing the glycolytic activity of breast cancer in a WTAP m6A-dependent manner (84). WATP has also been shown to improve the stability of HK2 mRNA via its interaction with the 3'-UTR m6A site, thereby mediating the glycolytic process and promoting the progression of gastric cancer (85). Therefore, high expression levels of WATP are associated with poor prognosis of patients with gastric cancer.

The regulation of FTO on tumor progression is not a case of simple inhibition or promotion. The expression of FTO has been shown to be abnormally increased in certain tumors (such as bladder cancer and endometrial cancer) to promote tumor progression, whereas overexpression of FTO in other tumors has the effect of inhibiting glycolysis, thereby inhibiting tumor cell proliferation and hindering tumor progression. A low expression level of FTO in papillary thyroid carcinoma leads to improvement in the stability and expression of apolipoprotein E (APOE) by enhancing the binding rate of IGF2BP2 to APOE mRNA, thereby promoting both the uptake of glucose by tumor cells and tumor growth (86). Taken together, the effects of FTO on tumor action may depend on the different downstream target molecules and the specific tissue environment.

Low expression levels of ALKBH5 have been found to be associated with poor prognosis in bladder cancer, as this

Table I. Role of m6A enzyme in tumor proliferation, invasion and migration.

m6A	Cancer type	Role	Regulated target	(Refs.)
METTL3	Bladder cancer	Oncogene	AFF4/NF-κB/MY	(30)
	Bladder cancer	Oncogene	pri-miR221/222	(31)
	Colorectal cancer	Oncogene	SOX2	(32)
	Gastric cancer	Oncogene	ZMYM1	(33)
METTL14	Pancreatic cancer	Oncogene	PERP	(34)
	Colorectal cancer	Tumor suppressor	XIST	(35)
	Colorectal cancer	Tumor suppressor	SOX4	(36)
	Gastric cancer	Tumor suppressor	PI3K/AKT/mTOR	(37)
	Stomach adenocarcinoma	Tumor suppressor	PTEN	(38)
WTAP	Hepatocellular carcinoma	Oncogene	ETS1	(40)
KIAA1429	Hepatocellular carcinoma	Oncogene	GATA3	(18)
	Lung adenocarcinoma	Oncogene	MUC3A	(41)
METTL16	Hepatocellular carcinoma	Oncogene	eIF3a/b	(42)
FTO	Breast cancer	Oncogene	miR-181b-3p	(43)
	Bladder cancer	Oncogene	MALAT1	(44)
	Endometrial cancer	Oncogene	HOXB13	(45)
ALKBH5	Epithelial ovarian cancer	Oncogene	HOXA10, JAK2	(47)
	Epithelial ovarian cancer	Oncogene	BCL-2	(48)
	Breast cancer	Oncogene	NANOG	(49)
	Gastric cancer	Oncogene	NEAT1	(50)
	Pancreatic cancer	Tumor suppressor	WIF-1	(51)
	Pancreatic cancer	Tumor suppressor	PER1	(52)
YTHDF1	Ovarian cancer	Oncogene	EIF3C	(53)
YTHDF2	Glioblastoma	Oncogene	MYC, IGF2BP3	(54)
	Glioblastoma	Oncogene	LXRA, HIVEP2	(55)
	Prostate cancer	Oncogene	LHPP, NKX3-1	(56)
	Hepatocellular carcinoma	Oncogene	OCT4	(57)
	Hepatocellular carcinoma	Tumor suppressor	EGFR	(58)
YTHDF3	Breast cancer	Oncogene	ST6GALNAC5, GJA1, EGFR	(59)
	Colorectal cancer	Oncogene	GAS5	(60)
YTHDC1	Lung cancer	Oncogene	RBM4	(62)
YTHDC2	Lung cancer	Tumor suppressor	CYLD	(65)
IGF2BP1	Endometrial cancer	Oncogene	PEG10	(68)
IGF2BP2	Pancreatic cancer	Oncogene	DANCR	(69)
	Colorectal cancer	Oncogene	YAP	(70)
	Head and neck squamous cell carcinoma	Oncogene	Slug	(71)
IGF2BP3	Colon cancer	Oncogene	CCND1, VEGF	(72)
	Bladder cancer	Oncogene	JAK/STAT	(73)

METTL3/4, methyltransferase-like 3/4; WTAP, Wilms tumor 1-associated protein; FTO, fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate-dependent dioxygenase homolog 5; IGF2BP1/2/3, IGF2 binding protein 1/2/3; YTHDF1/2/3, YTH domain family protein 1/2/3; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; eIF3, eukaryotic initiation factor 3; RBM15/RBM15B, RNA-binding motif protein 15/RNA-binding motif protein 15B; VIRMA, Vir like M6A methyltransferase associated; HAKAI, E3 ubiquitin-protein ligase Hakai; ZC3H13, zinc finger CCCH domain-containing protein 13; AFF4, AF4/FMR2 family member 4; SOX2, SRY (sex determining region Y)-box 2; ZMYM1, zinc finger MYM-type containing 1; PERP, p53 effector related to PMP-22; XIST, X inactivation-specific transcript; SOX4, SRY-related high-mobility-group box 4; PTEN, phosphatase and tensin homologue; ETS1, ETS proto-oncogene 1; MUC3A, mucin 3A; eIF3a/b, eukaryotic initiation factor 3a/b; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HOXA10, homeobox A10; NEAT1, nuclear paraspeckle assembly transcript 1; WIF-1, Wnt inhibitory factor 1; PER1, period circadian regulator 1; EIF3, eukaryotic initiation factor 3; LXRA, liver X receiver α; HIVEP2, human immunodeficiency virus type I enhancer binding protein 2; LHPP, phospholysine phosphohistidine inorganic pyrophosphate phosphatase; NKX3-1, NK3 homeobox 1; OCT4, octamer-binding transcription factor 4; EGFR, epidermal growth factor receptor; GASS, growth arrest-specific 5; RBM4, RNA-binding protein 4; YAP, Yes-associated protein; PEG10, paternally expressed gene 10; DANCR, differentiation antagonizing non-protein coding RNA; CCND1, cyclin D1.

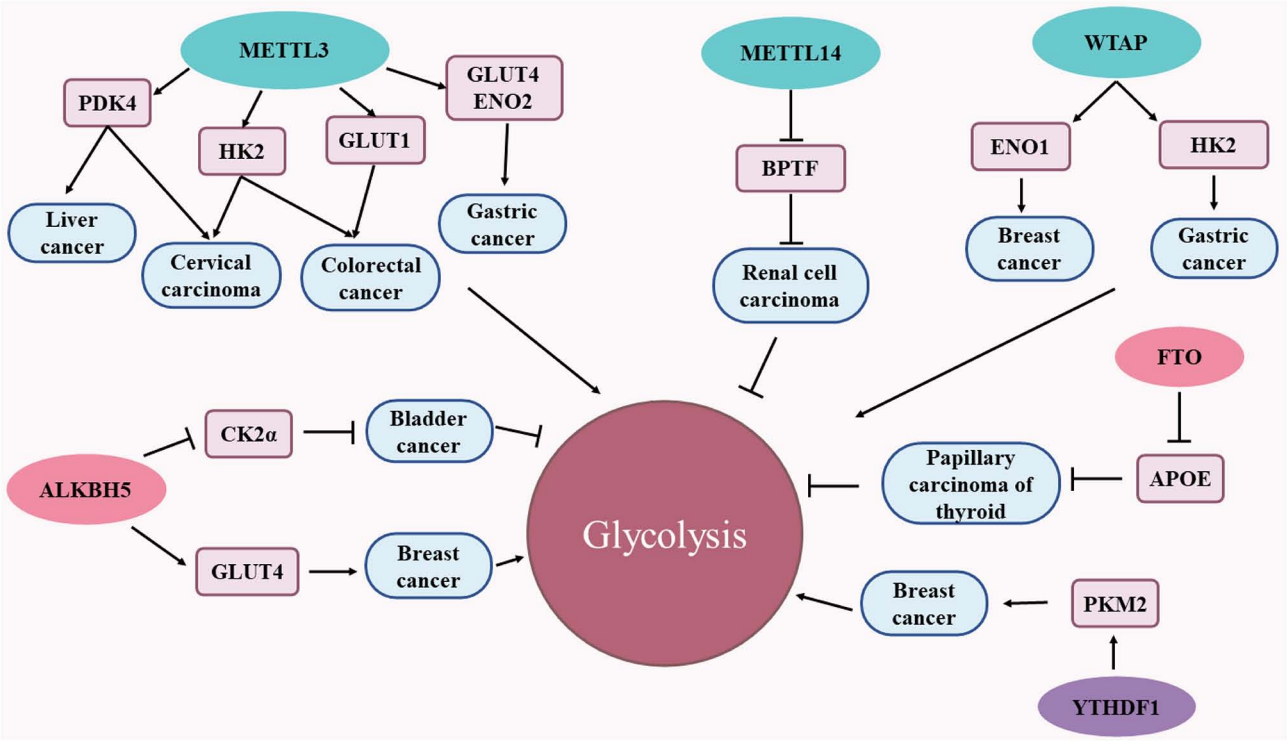

Figure 2. m6A methylases that participate in cancer glycolytic metabolic pathways. Cancer cells rely on glycolytic pathways to meet their energy needs for growth and proliferation, and m6A-associated enzymes participate in the cancer glycolytic pathway. The m6A methyltransferase METTL3 is able to promote glycolysis and tumor progression through m6A modification-mediated downstream targets (PDK4, GLUT1, HK2, GLUT1, GLUT4 and ENO2). METTL14 inhibits glycolysis and tumor progression by accelerating the degradation of BPTF mRNA. WTAP is able to mediate the glycolytic process of tumors and promote tumor progression through either upregulating ENO1 expression or enhancing the stability of HK2 mRNA in an m6A-dependent manner. ALKBH5 has a dual effect on the glycolytic pathway, on one hand attenuating CK2α, and on the other hand increasing the stability of GLUT4 mRNA, thereby promoting the glycolysis of breast cancer cells. FTO inhibits glycolysis and thyroid cancer growth by reducing the stability of apoE mRNA in an m6A-dependent manner. Finally, YTHDF1 enhances glycolysis by improving the protein translation of PKM2, thereby promoting the progression of breast cancer. apoE, apolipoprotein E; METTL3/4, methyltransferase-like 3/4; WTAP, Wilms tumor 1-associated protein; FTO, fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate-dependent dioxygenase homolog 5; PDK4, pyruvate dehydrogenase kinase 4; GLUT1/4, glucose transporter 1/4; YTHDF1/2/3, YTH domain family protein 1/2/3; HK2, hexokinase 2; ENO2, enolase 2; BPTF, bromodomain PHD finger transcription factor; CK2α, casein kinase 2α; m6A, N6-methyladenosine; PKM2, pyruvate kinase M2; ENO2, enolase 2.

reduces the glucose utilization of, and lactate production by, tumor cells via attenuating the mRNA stability of casein kinase 2α and inhibiting glycolysis in an m6A-dependent manner, ultimately inhibiting not only tumor progression, but also enhancing the sensitivity of bladder cancer cells to chemotherapeutic agents such as cisplatin (87). By contrast, the upregulation of ALKBH5 expression not only increases resistance to HER2-targeted therapy in patients with HER2-positive breast cancer, but it also promotes the m6A demethylation of GLUT4 mRNA under the influence of YTHDF2 to increase GLUT4 mRNA stability, thereby promoting glycolysis in breast cancer cells (88).

In addition to methylases and demethylases that participate in tumor cell glycolysis, m6A-binding proteins also have an important role in the glycolytic process. YTHDF1 is a key driving factor for the development of breast cancer, able to enhance the proliferation and invasion of breast cancer cells and inhibit apoptosis. In addition, YTHDF1 can enhance glycolysis through increasing the protein translation of PKM2, thereby promoting the progression of breast cancer (89).

Therefore, abnormal expression of m6A-associated proteins in tumor cells is able to affect glycolysis, leading to changes in glucose uptake and lactic acid production, affecting ATP production, and ultimately influencing the progression of tumors.

m6A and lipid metabolism. For tumor cells, fatty acids are also an important source of energy and lipid metabolism also has an important role in tumor progression (90). For mammals, there are two main sources of lipids: One through food intake (exogenous), and the other by means of *de novo* lipid synthesis (endogenous), where *de novo* lipid synthesis is also an important marker of tumor metabolism. Fatty acids are important products of lipid metabolism that are essential for tumor cell proliferation, and thus, reducing fatty acid levels by disrupting their production and increasing their degradation may provide an effective approach for tumor treatment (91). The lipid metabolism has been shown to improve the energy source for the growth and proliferation of tumor cells, improve the invasive and migratory capabilities of tumors and also fulfill an important role in tumor progression (92,93). Overall, it is indicated that the m6A modification also exerts an important role in the lipid metabolism of tumors.

The methylase METTL3 has been observed to promote the upregulation of the expression of LINC00958, an adipogenesis-associated lncRNA, through mediated m6A modification, which subsequently led to increased proliferation, invasion

and migration of hepatocellular carcinoma cells, and increased adipogenesis via the miR-3619-5p/HDGF pathway, driving the progression of hepatocellular carcinoma (94).

The demethylase FTO has also been indicated to be involved in regulating lipid metabolism in the liver, which is dependent upon m6A demethylation to promote the generation of large amounts of fat in liver cells, consequently leading to large amounts of lipid deposition (95). In hepatocellular carcinoma cells, deletion of FTO leads to decreased stability and downregulation of the expression level of fatty acid synthase mRNA, a lipid metabolism gene that is influenced by m6A modification, which further downregulates the protein expression levels of acetyl coenzyme A carboxylase and ATP-citrate lyase, ultimately inhibiting *ab initio* lipid synthesis and promoting tumor cell apoptosis, impeding the progression of hepatocellular carcinoma (96). In addition, FTO has also been shown to be involved in the regulation of lipid metabolism in esophageal cancer, and FTO may increase the formation of lipid droplets in esophageal cancer by promoting the translation efficiency of HSD17B11 through YTHDF1, thereby promoting the proliferation, migration and stemness of esophageal cancer cells and enhancing their tumorigenicity (97).

As the current understanding of the mechanisms associated with the role of m6A-associated enzymes in tumor lipid metabolism deepens, novel therapeutic ideas will be pursued for tumor treatment, and ultimately, new therapeutic strategies will be adopted to intervene with the lipid uptake of tumor cells, or to develop novel anti-cancer drugs by discovering new targets for intervention, thereby improving the already existing therapeutic interventions for tumors.

m6A and glutamine metabolism. In addition to the Warburg effect and fatty acid metabolism, another common alteration in tumor metabolism is increased glutamine metabolism. Glutamine metabolism exerts a positive regulatory effect on the tricarboxylic acid cycle and nucleotide and fatty acid biosynthesis in tumor cells (98). Glutamine, the most abundant amino acid in human blood, in its high-level state, provides a ready source of carbon and nitrogen for the growth of tumor cells (99). For tumor cells to continuously proliferate, this process is dependent on glutamine to meet the metabolic demands of the tumor cells; therefore, targeting glutamine catabolism has been a key research direction in tumor therapy. Recent studies have also identified the mechanism underlying the role of m6A-associated enzymes in glutamine metabolism.

When glutamine catabolism is inhibited, tumor cells are able to survive through activating autophagy, a process in which m6A serves an important role in the regulation of activating transcription factor 4 (ATF4). FTO was found to be upregulated upon inhibition of glutamine catabolism, which served to maintain the stability, prolong the half-life and upregulate the expression of ATF4 mRNA, subsequently promoting the transcription of DNA-damage-inducible transcript 4 and inducing inactivation of the mTOR signaling pathway, thereby promoting cellular autophagy and maintaining tumor survival and growth (100).

Deficiency of the tumor suppressor von Hippel-Lindau (VHL) is a hallmark feature of renal clear cell carcinoma, and glutamine has been shown to support the growth and survival of VHL-deficient renal clear cell carcinoma cells (101); however, FTO is highly expressed in VHL-deficient renal clear cell carcinoma cells and regulates the expression of the glutamine transporter protein SLC1A5 in an m6A-dependent manner, suggesting that FTO fulfills an important role in the metabolic reprogramming (glutamine metabolism) of VHL-deficient renal clear cell carcinoma through mediating SLC1A5 (102).

m6A readers are also involved in the regulation of tumor glutamine metabolism. YTHDF1, a potential oncogene, is highly expressed in the colorectum, subsequently leading to a decrease in tumor sensitivity to cisplatin, the underlying mechanism of which may be that YTHDF1 is able to bind directly to the 3'-UTR of glutaminase-1 (GLS1) mRNA, thereby promoting protein translation (103). Therefore, activation of the GLS1-glutamine metabolic axis mediated by YTHDF1 is a key step in YTHDF1-mediated cisplatin resistance in colorectal cancer, suggesting that inhibition of glutamine metabolism, in combination with cisplatin therapy, exerts a synergistic effect in the treatment of tumors. YTHDC2 was also found to exhibit antitumor activity in lung adenocarcinoma via promoting the degradation and decay of solute carrier family 1 member 5 (SLC7A1) mRNA in an m6A-dependent manner through the YTH structural domain and by inhibiting cystine uptake, resulting in impaired oxidation in lung adenocarcinoma cells and ultimately inhibiting tumor progression (104).

Since the growth and proliferation of tumor cells depend on glutamine metabolism, targeting glutamine metabolism may become a new strategy for tumor therapies.

5. Targeting m6A in ferroptosis

Ferroptosis, a recently discovered form of programmed cell death, is mainly characterized by iron-dependent reactive oxygen species production and the accumulation of lipid peroxidation products. Investigating ferroptosis, as a key tumor suppressor mechanism, therefore provides a new research direction for tumor treatment. A large number of studies have now revealed the regulatory mechanism of m6A in ferroptosis (Fig. 3).

System Xc-is a glutamate-cystine reverse transport system that includes two subunits, namely SLC7A11 and SLC3A2, and inhibition of system Xc-has been shown to induce ferroptosis (105,106). SLC7A11 is overexpressed in a variety of tumor types, and may promote tumor growth through inhibiting ferroptosis (107). SLC3A2, a chaperone protein of SLC7A11, may also support the function of SLC7A11, leading to the prevention of cellular lipid peroxidation (108).

METTL3 was found to stabilize SLC7A11 mRNA, which subsequently promotes its translation by recruiting the YTHDF1-mediated m6A modification, thereby promoting lung adenocarcinoma cell proliferation and inhibiting cellular ferroptosis (109). In hepatoblastoma, SLC7A11 mRNA is also regulated by METTL3 through the modification of m6A. Furthermore, METTL3/IGF2BP2 have not only been shown to enhance the stability of SLC7A11 mRNA through m6A modification, but they also upregulate its expression via inhibiting the process of deadenylation, thereby enhancing the ferroptosis resistance of the tumor cells (110).

In contrast to the tumor-promoting effect of METTL3, METTL14 frequently has a tumor-inhibiting role via inducing

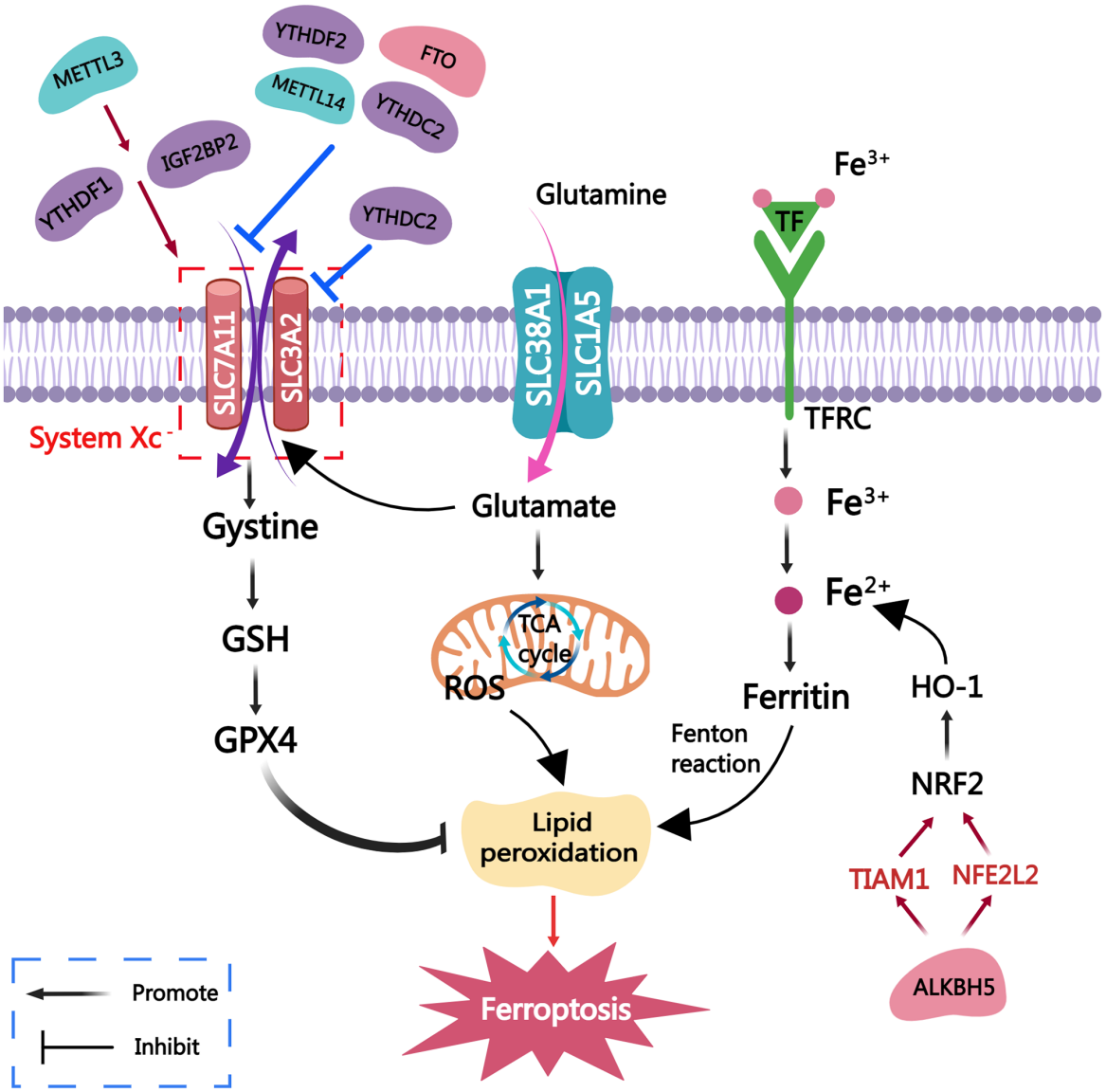

Figure 3. m6A methylases that participate in ferroptosis. Ferroptosis is a form of cell death characterized by an accumulation of $Fe2^{+}$ ions and lipid peroxide overload. The mechanism of ferroptosis is as follows: i) Iron ions are inputted into the cells, converted into divalent iron and accumulate in large amounts, promoting the occurrence of lipid peroxidation through the Fenton reaction; ii) the systemXc- system (SLC3A2+SLC7A11) is presented: The SystemXc^{-}-GSH-GPX4 axis, wherein GPX4 inhibits lipid peroxidation; iii) SLC38A1+SLC1A5: Glutamine enters the cell through glutamine transporters to generate glutamate, which enters the mitochondria and participates in the TCA cycle to generate mitochondrial ROS, thereby promoting ferroptosis. m6A-associated enzymes can participate in the ferroptotic pathway of tumors, thereby regulating tumor progression. METTL3 inhibits ferroptosis by enhancing the stability of SLC7A11 mRNA through YTHDF1 and IGF2BP2, respectively. METTL14, FTO, YTHDF2 and YTHDC2 inhibit SLC7A11, thereby inducing ferroptosis. YTHDC2 can also increase the sensitivity of tumor cells to ferroptosis by inhibiting SLC3A2. Finally, ALKBH5 induces ferroptosis by mediating the m6A-TIAM1-Nrf2/HO-1 signaling pathway, thereby hindering tumor progression. SLC3A2, solute carrier family 3 member 2; METTL3/4, methyltransferase-like 3/4; FTO, fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate-dependent dioxygenase homolog 5; IGF2BP1/2/3, IGF2 binding protein 1/2/3; YTHDF1/2/3, YTH domain family protein 1/2/3; GSH, glutathione; GPX4, GSH peroxidase 4; ROS, reactive oxygen species; m6A, N6-methyladenosine; TIAM1, TIAM Rac1 associated GEF 1; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; NFE2L2, NFE2 like bZIP transcription factor 2; TCA, tricarboxylic acid; TF, transferrin; TFRC, TF receptor.

ferroptosis. Under normoxic conditions, METTL14 targets the methylation of m6A at the 3'-UTR of SLC7A11 mRNA to promote the degradation of SLC7A11 mRNA. At the same time, YTHDF2 can also recognize SLC7A11 mRNA and promote its degradation, thereby inducing the occurrence of ferroptosis of tumor cells and inhibiting the progression of hepatocellular carcinoma (111).

The expression level of FTO has also been shown to be downregulated in papillary thyroid carcinoma, and this was negatively correlated with SLC7A11; therefore, FTO functions as a tumor suppressor gene. Overexpressed FTO was shown to inhibit SLC7A11 expression via mediating m6A methylation, thereby promoting the ferroptosis of thyroid papillary carcinoma cells and inhibiting tumor cell growth (112).

Similarly, the demethylase ALKBH5, which is downregulated in thyroid cancer, induces ferroptosis through mediating the m6A-TIAM Rac1 associated GEF 1-nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 signaling pathway, thereby hindering the progression of thyroid cancer (113).

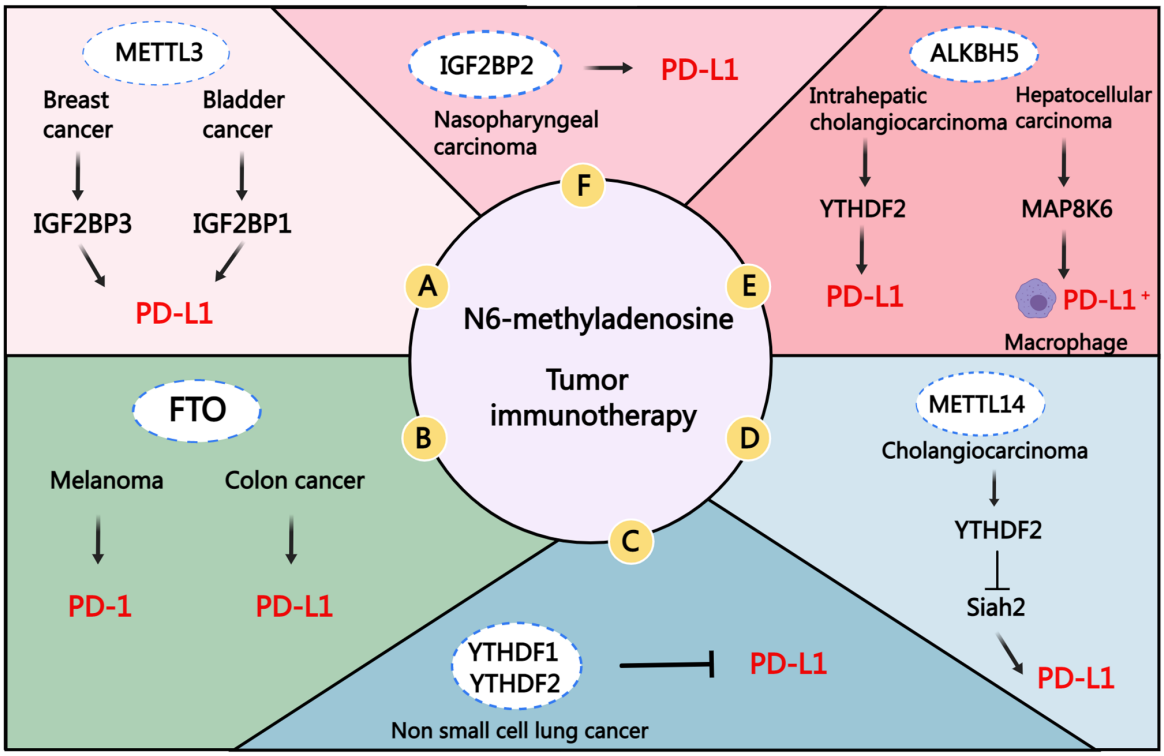

Figure 4. Role of m6A methylases in tumor immunotherapy. (A) METTL3 can inhibit anti-tumor T-cell activation through both IGF2BP3- and IGF2BP1-mediated PD-L1 mRNA stability and upregulation of its expression. (B) FTO can promote the expression of PD-1 and PD-L1 in an m6A-dependent manner. (C) The expression levels of YTHDF1 and YTHDF2 in non-small cell lung cancer are inversely proportional to PD-L1. (D) METTL14 mainly promotes the degradation of its downstream target Siah2 mRNA in a YTHDF2-dependent manner, thereby mediating immune escape. (E) The overexpression of ALKBH5 in intrahepatic cholangiocarcinoma maintains the stability of PD-L1 mRNA through YTHDF2. In hepatocellular carcinoma, ALKBH5 regulates MAP8K6 expression in an m6A-dependent manner and promotes the recruitment of PD-L1+ tumor-related macrophages. (F) IGF2BP2 can positively regulate the expression of PD-L1, and inhibition of the expression of IGF2BP2 can achieve the effect of inhibiting PD-L1. METTL3/4, methyltransferase-like 3/4; FTO, fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate-dependent dioxygenase homolog 5; IGF2BP1/2/3, IGF2 binding protein 1/2/3; YTHDF1/2/3, YTH domain family protein 1/2/3; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; m6A, N6-methyladenosine.

ALKBH5 also acts as an oncogenic factor in head and neck squamous cell carcinoma, mediating ferroptosis in tumor cells. Deletion of ALKBH5 not only significantly reduces the sensitivity of tumor cells to ferroptosis activators, but also induces the binding of NFE2 like bZIP transcription factor 2/NRF2 transcripts to IGF2BP2, thereby delaying its mRNA degradation and enhancing protein expression, ultimately achieving the goal of inhibiting ferroptosis in tumor cells (114).

YTHDF2 is also involved in the regulation of tumor ferroptosis as an m6A reader. YTHDF2 can form a cystathionine β-synthase (CBS) mRNA stabilizing lncRNA (CBSLR)/YTHDF2/CBS complex with the lncRNA CBSLR under hypoxic conditions, thereby destabilizing CBS mRNA in an m6A-regulated manner and preventing gastric cancer cells from entering into ferroptosis in oxygen-deficient states, which provides a target for the treatment of refractory hypoxic tumors (115).

In addition, the RNA-binding protein YTHDC2 also acts as a ferroptosis inducer in lung adenocarcinoma, where it is able to both directly inhibit SLC7A11 in an m6A-dependent manner and indirectly inhibit SLC3A2 through destabilizing HOXA13 mRNA, leading to an increase in the sensitivity of lung adenocarcinoma cells to ferroptosis (116).

Therefore, the m6A modification exerts a key role in mediating tumor ferroptosis, and in particular, the regulatory role mediated by m6A modification on SLC7A11 is of great research interest. Therefore, there is a need to further focus on mRNA m6A methylation and its functional role in the regulation of ferroptosis in numerous types of tumor, and to develop different therapeutic strategies for the different regulatory mechanisms of m6A-associated enzymes in tumor ferroptosis, which may also bring new insight into the treatment of tumors.

6. Targeting m6A in tumor immunotherapy

In recent years, the treatment of solid tumors is no longer merely limited to radiotherapy and chemotherapy, but immunotherapy has become one of the most common treatment methods, among which the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis is considered as the main target of immunotherapy (117). PD-1 is mainly expressed on activated T cells and it binds to PD-L1 in tumor cells and in the tumor microenvironment to mediate immunosuppression (118). Targeting PD-1/PD-L1 inhibition is a strategy for restoring the immune response of T cells to tumor cells, and this has provided a key breakthrough for certain types of tumor therapies (119). Furthermore, studies have identified that m6A methylation regulators may be key enzymes that regulate the expression of PD-1/PD-L1 and mediate immune infiltration (Fig. 4).

Macrophages are found in almost all tissues and were one of the first 'immune' cells to appear in evolution (120).

Macrophages are also prevalent in the solid tumor microenvironment, where immune evasion of the tumor cells occurs (121). It was found that deletion of METTL3 in bone marrow cells promotes tumor growth *in vivo*, even enhancing tumor invasion and metastasis, leading to the increased infiltration of tumor-associated macrophages and regulatory T cells in tumors, and an attenuation of PD-1 blockade therapy (122). In addition, it has been found that deletion of METTL3 in mouse T cells may affect the homeostasis and differentiation of naive T cells (123). Therefore, m6A modification is helpful for maintaining the homeostasis and function of immune cells, and this may open up a new avenue for tumor immunotherapy. PD-L1, as a downstream target of METTL3, is directly regulated by METTL3 in terms of the m6A modification of its mRNA. In addition, METTL3 has also been shown to upregulate PD-L1 expression and maintain its mRNA stability in an m6A-IGF2BP3-dependent manner, thereby inhibiting the activation of anti-tumor T cells and promoting immune escape of tumors (124). Therefore, studying the METTL3/IGF2BP3 axis is of great significance for tumor immunotherapy. METTL3 has also been shown to regulate immune escape in bladder cancer in an m6A-dependent manner according to the following mechanism: Activation of the JNK signaling pathway upregulates the expression of METTL3, thereby promoting tumor immune escape through regulating PD-L1 resistance to $CD8^+$ T-cell cytotoxicity and, in the process, the reader IGF2BP1 mediates the mRNA stability of PD-L1 and its expression level (125).

METTL14 is also able to mediate tumor immune escape according to a mechanism that depends on m6A modifications. In cholangiocarcinoma, METTL14 directly regulates its downstream target seven in absentia homolog 2 (Siah2) through promoting Siah2 mRNA degradation mediated via YTHDF2, leading to a decrease in Siah2 protein expression levels and stable PD-L1 protein expression, which thereby inhibits T-cell expansion-mediated immune escape (126).

FTO, as a cancer-promoting factor of melanoma, has been shown to promote the proliferation, invasion and migration of melanoma cells. The loss of FTO was found to lead to an increase in the m6A enrichment of PD-1 and a decrease in its stability, and YTHDF2 was subsequently shown to mediate its mRNA decay (127). In addition, FTO was also shown to regulate PD-L1 mRNA and its expression through m6A modification in colon cancer (128). Hence, inhibition of the FTO pathway combined with PD-1 blockade immunotherapy may provide a new research direction for the treatment of tumors.

In the immune microenvironment of intrahepatic cholangiocarcinoma, overexpression of ALKBH5 was found, on the one hand, to regulate the level of m6A modification in the 3'-UTR of PD-L1 mRNA and to maintain the stability of PD-L1 mRNA by YTHDF2; on the other hand, it may also upregulate the expression of PD-L1 in monocytes/macrophages and reduce the infiltration of bone marrow-derived suppressor-like cells, thereby providing a possible new approach for tumor immunotherapy (129). In hepatocellular carcinoma, ALKBH5 was shown to regulate MAP8K6 expression in an m6A-dependent manner, promoting the recruitment of $PD\text{-}L1^+$ tumor-associated macrophages (130). Therefore, ALKBH5 overexpressed in hepatocellular carcinoma likewise has a role in regulating the tumor immune microenvironment.

YTHDF1, as a reader of m6A-modified mRNA, is associated with immune cell infiltration in the tumor microenvironment and serves an important role in immune regulation; it can also regulate the expression level of immune checkpoint genes through different signal transduction pathways, thereby allowing the identification of ideal targets for immunotherapy and providing a theoretical basis for combined molecular targeting therapies (131). The deletion of YTHDF1 in dendritic cells was shown to lead to inhibition of the expression of lysosomal proteases, thereby attenuating antigen degradation and achieving improved cross-presentation and cross-activation of $CD8^+$ T cells (132). The expression levels of YTHDF1 and YTHDF2 in non-small cell lung cancer were found to be proportional to the number of tumor-infiltrating lymphocytes, and inversely proportional to PD-L1 expression, indicating that high expression of YTHDF1 and YTHDF2 in non-small cell lung cancer is a predictor of improved prognosis for patients with tumors (133).

In hypopharyngeal carcinoma, inhibition of IGF2BP2 expression led to inhibition of PD-1/PD-L1, whereas inhibiting PD-L1 also leads to downregulation of IGF2BP2 expression levels, thereby inhibiting tumor growth (134). Although the mechanism of action has yet to be fully elucidated, targeting IGF2BP2 or using PD-L1 inhibitors may provide an effective means for the treatment of hypopharyngeal cancer.

In general, it has been shown that the association of m6A-related enzymes with the tumor immune system is crucial for the treatment of clinical tumors. However, at the present time, there remains a lack of systematic and comprehensive studies on the roles of m6A-associated enzymes in the tumor immune microenvironment, and their impact on human tumor immunotherapy. More detailed experimental studies are required to explore the potential mechanisms of m6A-associated enzymes in human tumor immunotherapy, and to provide a solid theoretical basis and novel insight for immunotherapy of tumors.

7. Potential clinical applications for targeting m6A-associated proteins

In recent years, the findings of studies associated with the mechanism of action of m6A-related proteins in tumor progression have led to the realization that m6A-associated proteins may be used as cancer therapeutic targets and this insight has motivated an increasing number of researchers to investigate their clinical applications (Fig. 5).

STM2457, a potent and selective inhibitor of METTL3, was shown to hinder the development of acute myeloid leukemia through catalytically targeting the inhibition of METTL3 to achieve certain therapeutic effects (135). In addition, for intrahepatic cholangiocarcinoma with high expression of METTL3, treatment of intrahepatic cholangiocarcinoma cells with STM2457 led to inhibition of the proliferation and enhanced rates of apoptosis (136). Therefore, STM2457, as a METTL3 inhibitor with anti-cancer cell-proliferation potential, may be used to treat cancers with high METTL3 expression, bringing new hope for the treatment of such tumors.

Given the pro-cancer role mediated by FTO in tumors, the development of targeted FTO inhibitors also has broad potential for cancer therapy. FB23 and FB23-2 are small-molecule

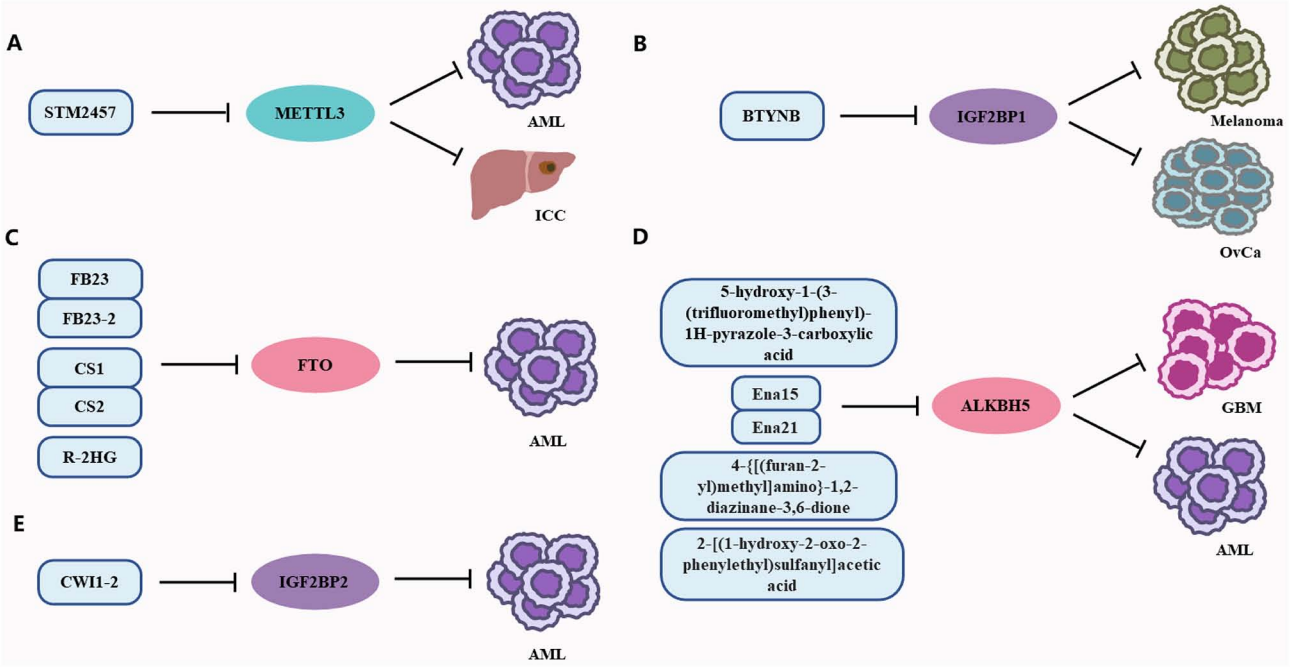

Figure 5. Inhibitors targeting m6A-associated proteins for cancer therapy. (A) As a potent and selective METTL3 inhibitor, STM2457 is able to impair the progression of AML and ICC by targeting METTL3. (B) BTYNB can effectively inhibit the proliferation of OvCa and melanoma cells expressing IGF2BP1. (C) FB23, FB23-2, CS1, CS2 and R-2HG, as FTO inhibitors, can exert anti-leukemia activity by inhibiting FTO activity. (D) 5-Hydroxy-1-[3-(trifluorome thyl) phenyl]-1H-pyrazole-3-carboxylic acid (20m) is a highly selective inhibitor of ALKBH5. The inhibitors Ena15 and Ena21 can inhibit the proliferation of GBM-derived cell lines by inhibiting the activity of ALKBH5. Finally, the inhibitors 2-[(1-hydroxy-2-oxo-2-phenylethyl)sulfonyl]acid and 4-{[(furan-2-yl) methyl]amino}-1,2-diazinane-3,6-dione can inhibit the proliferation of leukemia cells by inhibiting ALKBH5. (E) The small-molecule compound CWI1-2 can inhibit the carcinogenic effect of IGF2BP2 and inhibit the progression of acute myeloid leukemia. FTO, fat mass and obesity-associated protein; ALKBH5, α-ketoglutarate-dependent dioxygenase homolog 5; IGF2BP1/2/3, IGF2 binding protein 1/2/3; METTL3/4, methyltransferase-like 3/4; OvCa, ovarian cancer; GBM, glioblastoma multiforme; AML, acute myeloid leukemia; ICC, intrahepatic cholangiocarcinoma; STM2457, a specific small molecule inhibitor of METTL3; FB23, FTO demethylase inhibitor FB23; FB23-2, FTO demethylase inhibitor FB23-2; CS1, FTO demethylase inhibitor CS1; CS2, FTO demethylase inhibitor CS2; R-2HG, R-enantiomer of 2-hydroxyglutarate; Ena15 and Ena21, ALKBH5 inhibitor; BTYNB, 2-{[(5-bromo-2-thienyl)methylene]amino} benzamide; CWI1-2, small molecule inhibitors of IGF2BP2.

FTO inhibitors and meclofenamic acid derivatives have been developed that exert anti-proliferative effects and are effective therapeutic strategies for the treatment of acute myeloid leukemia (137). A previously published study demonstrated how computer screening and the experimental validation of compounds in the National Cancer Institute Developmental Therapeutics Program library led to the identification of two small molecules with FTO-inhibiting activity, namely CS1 and CS2, which also exerted anti-leukemic effects (138). In addition, R-2-hydroxyglutarate was also found to inhibit the proliferation of leukemic cells, exerting anti-leukemic effects via inhibiting FTO activity (139). Therefore, the research goal is to confirm the potential therapeutic effects of these FTO inhibitors in other types of cancer with high FTO expression.

What is known about the mechanism underlying the action of the demethylase ALKBH5 in cancer indicates that ALKBH5 is expected to become an important target for cancer treatment, and thus, it is imperative to develop an effective and selective ALKBH5 inhibitor. It was found that 5-hydroxy-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid exhibited high selectivity for ALKBH5 and its administration led to inhibition of m6A demethylation (140), although further experiments are required to confirm its role in cancer therapy. Through high-throughput screening, two novel inhibitors of ALKBH5, Ena15 and Ena21, were identified to inhibit cell proliferation of glioblastoma multiforme-derived cell lines via inhibiting ALKBH5D activity, thereby exerting anti-tumor effects and impeding tumor progression (141). Furthermore, 2-[(1-hydroxy-2-oxo-2-phenylethyl)sulfanyl]acetic acid and 4-{[(furan-2-yl)methyl]amino}-1,2-diazinane-3,6-dione are ALKBH5 inhibitors that were also identified through high-throughput screening, which exert inhibitory effects on the proliferation of leukemia cells at low micromolar concentrations (142), once again providing a new approach for the development of anti-cancer therapies.

IGF2BP1 frequently acts as a cancer-promoting factor, which exerts an active role in the progression of cancer. It has been reported that the IGF2BP1 inhibitor BTYNB not only inhibits the proliferation of melanoma and ovarian cancer cells by breaking the bond between IGF2BP1 and MYC mRNA (143), but also inhibits the proliferation of tumor cells and the growth of solid tumors by reducing the binding of IGF2BP1 to E2F1 mRNA (144). It has been observed that BTYNB, as a special type of IGF2BP1 inhibitor, is able to inhibit tumor cell proliferation through blocking the IGF2BP1-RNA association, which brings new hope for the treatment of IGF2BP1-driven tumors.

A recent study screened CWI1-2, a small-molecule compound that is able to inhibit the pro-cancer effects of IGF2BP2, and demonstrated through a series of *in vivo* and

ex vivo experiments that it exhibited appreciable anti-leukemic effects, indicating the great potential of CWI1-2 as an anti-leukemia drug (145).

In general, the targeted clinical application of m6A-associated proteins remains in the initial stages of research. Therefore, there is an urgent need to perform additional studies to increase the current understanding of the functions and mechanisms of m6A-associated proteins in cancer regulation, so as to provide a solid theoretical basis for the development of drugs targeting m6A-associated proteins. Furthermore, the role of targeting m6A-associated proteins may be further explored in terms of synergistic cancer therapies, combining them with traditional drugs for cancer treatment. In conclusion, the development and screening of efficient and selective inhibitors of m6A-associated proteins for use in anti-cancer therapy through extensive basic and clinical experiments should bring new promise and hope for the future of cancer treatment.

8. Conclusions and future prospects

In recent years, research on the m6A methylation of RNA has helped improve our understanding of the potential underlying mechanisms and its functional role in tumor progression and tumor immunotherapy. The present review has summarized the basic functional characteristics of m6A-associated proteins, outlining the effects of m6A-associated proteins on the processes of tumor cell proliferation, migration and invasion, the regulation of tumor metabolism, the potential mechanisms involved in ferroptosis and their impact on tumor immunotherapy, through which targeting m6A has been highlighted as a promising new avenue for future cancer treatment.

Of note, the abnormal m6A methylation levels exhibited by different tumor tissues have provided insight into the dual role of m6A methylation: i) The same m6A-associated protein may exert different roles in different tumor tissues; ii) different m6A-associated proteins fulfill different roles in the same tumor tissue; iii) certain genes exert a pro-cancer role following m6A methylation, while others exert a pro-cancer role after demethylation; iv) the same m6A-associated protein may fulfill different roles in regulating different downstream targets in the same tumor tissue. Therefore, a deep understanding of the complex regulatory mechanisms of m6A methylation should provide a solid theoretical basis for predicting patient prognosis, investigating targeted therapies for m6A-associated proteins and for improving anti-PD-1/PD-L1 responsiveness.

Although a large number of studies on m6A methylation modifications have been published to date, the current knowledge in this area remains incomplete. More in-depth and comprehensive studies on m6A-associated proteins are required to reveal their underlying biological mechanisms in tumor development and to establish how they regulate the tumor immune microenvironment. In addition, a deeper understanding of the dual roles served by m6A in cancer progression (i.e., cancer promotion and cancer inhibition) is required, and our hope is that more efficient and selective drugs targeting m6A-associated proteins will be developed and screened for cancer treatment in the near future in order to improve patient prognosis.

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Authors' contributions

XP, YTW, QJ and SQF conceived the study and wrote the manuscript. HZ, LMC, HWT and MTW collated the data. XW and MX (corresponding author) revised and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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