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Decoding m^{6}A mRNA methylation by reader proteins in cancer

Bing Han [a], Saisai Wei [a], Fengying Li [a], Jun Zhang [a], Zhongxiang Li [b], Xiangwei Gao [a,*]

[a] Sir Run-Run Shaw Hospital, School of Public Health, Zhejiang University School of Medicine, Hangzhou, 310058, China
[b] Medical Research Institute, Baoan Women's and Children's Hospital, Jinan University, Shenzhen, 518133, China

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ABSTRACT

N^6-methyladenosine (m^{6}A), the most prevalent internal modification in eukaryotic mRNAs, regulates gene expression at the post-transcriptional level. The reader proteins of m^{6}A, mainly YTH domain-containing proteins, specifically recognize m^{6}A-modified mRNAs and regulate their metabolism. Recent studies have highlighted essential roles of m^{6}A readers in the initiation and development of human cancers. In this review, we summarize recent findings about the biological functions of YTH domain proteins in cancers, the underlying mechanisms, and clinical implications. Gene expression reprogramming by dysregulated m^{6}A reader proteins offers potential targets for cancer treatment, while targeted m^{6}A editors and readers provide tools to manipulate m^{6}A metabolism in cancers.

1. Introduction

Chemical modifications of RNA are critical for gene expression at the post-transcriptional level, which subsequently induce changes in biological outputs. In particular, the N^6-methyladenosine (m^{6}A) modification on RNAs, methylation at the sixth position nitrogen atom of adenosine (A), is an essential regulator because of its high abundance: it has been found in 0.1–0.4 % of messenger RNA (mRNA) adenosine residues in diverse eukaryotic cells [1–3]. Despite the early discovery in various cellular mRNAs in the 1970s, the distribution of m^{6}A was recently clarified with the development of detecting methodologies (m^{6}A-seq and its derivatives) [4,5]. These methods allow analyzing m^{6}A distribution at the transcriptomic level, opening up the era of "epitranscriptomics". Mapping of m^{6}A in different organisms revealed a highly conserved feature of this modification. A consensus motif of m^{6}A modification, RRACH ([G/A/U][G/A]m^{6}AC[U/A/C]), has been identified by the m^{6}A-seq data [5,6]. As for the exact positions, m^{6}A is enriched around stop codons and in the 3′ untranslated regions (3′ UTRs) [4,5]. In addition to methodological breakthrough, the characterization of its enzyme system further brought this modification into the spotlight [7]. It is now known that the m^{6}A modification is dynamically regulated by methyltransferases ('writers') and demethylases ('erasers') [8,9]. The writers, including core methyltransferase components (METTL3 and METTL14) and their cofactors (WTAP, RBM15, HAKAI, VIRMA, and ZC3H13), promote the deposition of m^{6}A on mRNAs [10]. The reversibility of m^{6}A relies on erasers, including FTO and ALKBH5, leading to the removal of m^{6}A modifications for a balanced equilibrium [7,9].

2. "Reader" proteins regulate the fate of m^{6}A-modified mRNAs

m^{6}A methylation alters Watson-Crick base pairing strength, RNA secondary structure, or protein-RNA interactions, which in turn affects gene expression by modulating almost all aspects of RNA metabolism, including processing, localization, translation, and decay [11–13]. Recognition by proteins is most widely studied mechanism, and the m^{6}A "reader" proteins directly regulate RNA fate. Combined approaches involving RNA affinity chromatography and mass spectrometry have been used to identify several m^{6}A readers, including YT521-B homology domain-containing proteins (YTHDF1-3 and YTHDC1-2) [5], insulin-like growth factor 2 (IGF2) mRNA-binding proteins (IGF2BP1-3) [14], FMR1 [15], and heterogeneous nuclear ribonucleoprotein (HNRNP) protein family members [16,17]. These reader proteins decode m^{6}A and decide the metabolic fate of modified mRNAs, indicating that they are crucial in the regulation of RNA metabolism and post-transcriptional gene expression.

m^{6}A readers process RNA at least through 3 mechanisms: selectively binding, weakening the cognate binding proteins, altering the secondary structure of RNA and RNA-protein interactions [8]. Highly conserved YTH domain proteins selectively bind to m^{6}A modifications with high affinity and a large binding interface, further altering the secondary structure [18]. Interestingly, these m^{6}A readers have distinguishing

* Corresponding author.
E-mail address: xiangweigao@zju.edu.cn (X. Gao).

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features of RNA processing. YTHDF1 has recently been extensively studied as a cytoplasmic m^{6}A reader. YTHDF1 binds to m^{6}A at exact G[G > A](m^{6}A)C sites and promotes translation initiation by interacting with initiation factors and ribosomes [19]. As a homologous gene of YTHDF1, YTHDF2 was identified by RNA immunoprecipitation (RIP) and photoactivatable ribonucleotide crosslinking and immunoprecipitation (PAR-CLIP) experiments to have a conserved G(m^{6}A)C[U > A] motif, and this protein plays an important role in RNA decay by recruiting the mRNAs to processing bodies (P-bodies) [20]. With similar sequence identity to YTHDF2, YTHDF3 facilitates m^{6}A-containing mRNA translation and decay together with YTHDF1 and YTHDF2 [21,22]. YTHDC2, another cytoplasmic YTH family member, regulates mRNA stability by interacting with the 5′-3′ exoribonuclease XRN1 and enhances the translation efficiency of its targets in spermatogenesis and oogenesis [23,24]. However, IGF2BPs represent a different facet of the m^{6}A reading process, mainly promoting mRNA stability and translation by recognizing the consensus GG(m^{6}A)C sequence [14]. As for nuclear-specific m^{6}A readers, YTHDC1 preferentially recognizes the GG(m^{6}A)C sequence and mainly functions in mRNA splicing and nuclear export [25–27]. Heterogeneous nuclear ribonucleoprotein G and C (HNRNPG/HNRNPC) are other two nuclear readers that bind m^{6}A to regulate alternative splicing [16,28,29]. Additionally, another hnRNP family protein, HNRNPA2B1, binds to m^{6}A in the pri-miRNA to facilitate miRNA processing by recruiting a microprocessor [17] (Fig. 1).

3. Manipulating YTH domain protein-regulated m^{6}A metabolism

Recently developed m^{6}A editors offer a way to manipulate m^{6}A specifically in individual transcripts [30–32]. Based on CRISPR/Cas system, these editors compose a methyltransferase or a demethylase fused with a catalytically inactive Cas proteins (dCas9 or dCas13). With the help of guide RNAs (gRNAs), site-specific m^{6}A incorporation or demethylation in specific transcripts could be achieved (Fig. 2). Studies using these editors demonstrated that single site methylation in different mRNA regions may play different roles, either promoting mRNA translation or degradation. In addition to these m^{6}A editors, targeted m^{6}A readers have also been developed by fusing m^{6}A reader proteins, YTHDF1 or YTHDF2, to dCas13b [33]. The fusion proteins can target the reader to specific RNA of interest using gRNA (Fig. 2). Tethering targeted mRNA with the fusion proteins can trigger enhanced protein

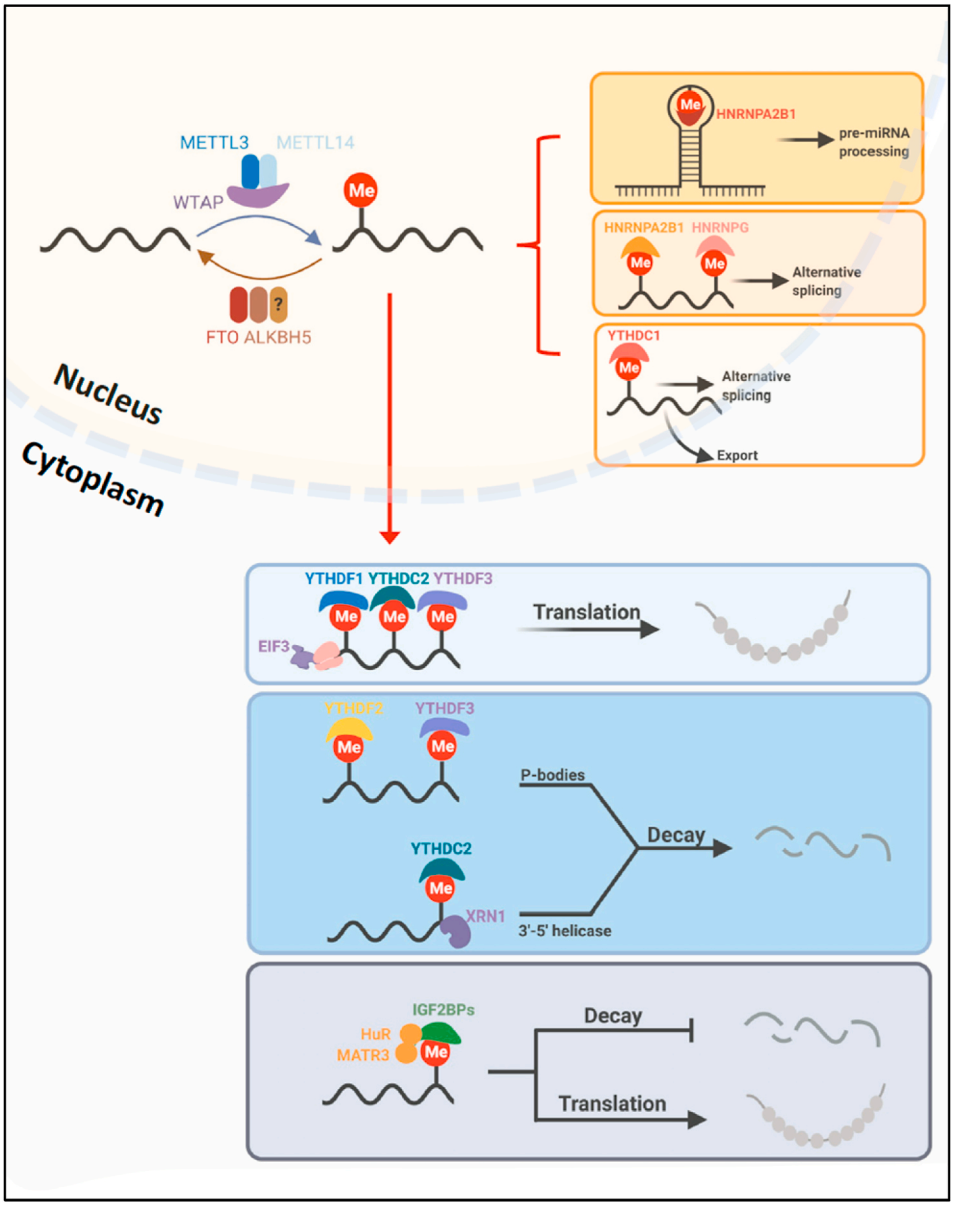

Fig. 1. The functions of m^{6}A reader proteins in mRNA metabolism.
The m^{6}A reader proteins recognize m^{6}A and determine target mRNA fate. The nuclear m^{6}A reader proteins YTHDC1, HNRNPG, and HNRNPA2B1 regulate mRNA splicing, nuclear export, and pre-miRNA processing, while the cytosolic m^{6}A reader proteins YTHDF1-3, YTHDC2, and IGF2BP1-3 regulate mRNA translation and decay.

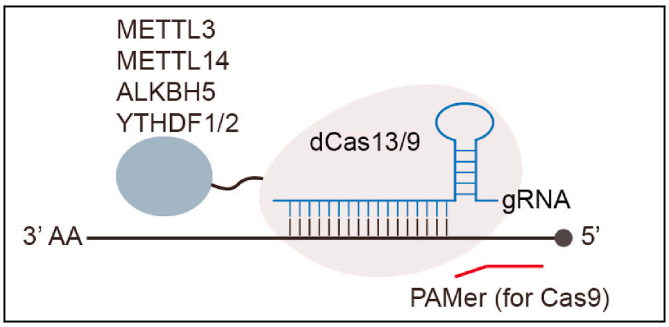

Fig. 2. Schematic of targeted m^{6}A editors and readers.
Targeted m^{6}A editors or readers have been developed by fusing m^{6}A writers, erasers, or readers to dCas13b/dCas9. The fusion proteins can target the mRNAs of interest with the help of gRNA and regulate their metabolism.

production or RNA degradation. The development of dCas-based targeted m^{6}A editors or readers reveal the effect of individual m^{6}A modifications and dissect their functional roles.

4. The roles of YTH domain proteins in cancer initiation and development

Abnormal epigenetic regulation contributes to cancer initiation and development, during which m^{6}A has gained increasing attention in cancer biology [34–36]. m^{6}A modification affects many cancer processes through writers, erasers and readers, such as cancer initiation, progression, metastasis, therapeutic response and cancer relapse [35]. For m^{6}A readers, accumulated evidence has shown that YTH domain proteins have essential roles in various complicated cancer pathogenesis. Because of the various RNA fate outcomes mediated by these readers, the m^{6}A machinery can play either oncogenic or tumor-suppressor roles in different cancer contexts. YTHDF1/3 and YTHDC2 are usually critical in promoting oncogene translation and thus act as positive tumor markers. However, YTHDF2 is reported to have dual roles in cancers that depend on the degradation of its target mRNAs. We briefly summarized the recent studies on the functions of YTH domain proteins in various cancers (Table 1). The dysregulation of m^{6}A readers in human cancers highlights the potential of using these proteins as new biomarkers and therapeutic targets in clinical practice.

5. Aberrant expression of YTH domain proteins in cancers

Emerging data have suggested that aberrant expression of YTH proteins in many types of cancers (Table 1) could be strongly associated with cancer progression and treatment outcomes. Many studies have shown an increase of YTHDF1 expression in cancers, indicating a positive correlation with cancer pathogenesis (Table 1). However, how YTHDF1 expression programs cells to adapt to long-term cancer environmental changes remains largely unknown. DNA copy number alterations [38] or transcriptional regulation [37] are both suspected to account for the overexpression of YTHDF1 in certain cancers. For example, in colorectal cancer (CRC), the oncogenic transcription factor c-Myc was shown to be associated with the 5′ region of the transcription start site of the YTHDF1 gene, indicating that c-Myc promotes YTHDF1 expression in CRC cells. Posttranscriptional regulation is also a key part of controlling YTHDF1 expression. In the intestine, the activated Wnt/APC signaling pathway promotes YTHDF1 translation by interacting with its 5′ UTR [39]. MiR-376c was reported to directly target the 3′UTR of YTHDF1 in non-small-cell lung cancer (NSCLC) cells [40]. Moreover, YTHDF1 could be regulated by USF1 and c-Myc at both the mRNA and protein levels in hepatocellular carcinoma (HCC) [49]. Despite the fact that YTHDF1 is dysregulated in cancers or at least can be a risk factor for cancer initiation and prognosis, future research needs to identify the upstream regulators of YTHDF1.

YTHDF2 has been found to participate in many cancers and might be associated with cancer progression. Interestingly, YTHDF2 expression is markedly inconsistent: it is upregulated in some types of cancers and downregulated in others. For example, YTHDF2 is highly expressed in bladder cancer, glioblastoma, acute myeloid leukemia (AML), lung cancer, ovarian cancer and prostate cancer but expressed at low levels in gastric cancer. Furthermore, YTHDF2 can act as either an oncogene or a tumor suppresser in HCC. Similar to the situation for other m^{6}A readers, evidence of how YTHDF2 responds to the cancer microenvironment is still limited. Hypoxia has been identified as a key driver of low YTHDF2 expression in HCC, and induction of HIFs, such as HIF-1α and HIF-2α, has been proven to mediate and enhance YTHDF2 function [78,79]. Recently, miRNAs have also been revealed as regulators of YTHDF2 expression. Luciferase reporter assays and statistical analysis confirmed that YTHDF2 is a direct target gene of miR-145 in ovarian cancer [86] and miR-495/miR-493-3p in prostate cancer [88,89].

6. YTH proteins in colorectal cancer

Colorectal cancer (CRC) is the third leading cause of cancer-related death in both men and women worldwide. However, many cancer cases and deaths could be prevented with appropriate screening and surveillance, which indicates the high clinical need for precise tumor biomarkers and therapeutic targets. m^{6}A related genes are found abundantly expressed in colon cancer, including reader protein YTHDC1 and HNRNPC [94]. Recently, most related studies have indicated YTHDF1 as a potential oncogene in CRC. Given that aberrant Wnt/β-catenin signaling is the driving force for intestinal tumorigenesis, some studies have focused on how YTHDF1 interacts with this pathway. The studies revealed that YTHDF1 is upregulated in CRC tissues versus normal tissues [39–41]. Deletion of the YTHDF1 gene in mouse intestinal stem cells (ISCs) induces tumor shrinkage and prolongs survival by blocking the Wnt signaling pathway [39]. In addition to playing a role in ISCs, YTHDF1 is also involved in promoting cancer stem-cell like activity by enhancing Wnt activity, which further regulates tumorigenicity in human CRC [40]. According to The Cancer Genome Atlas (TCGA) database, the expression of YTHDF1 in CRC also shows a positive correlation with an important Wnt target gene, c-Myc. Mechanistically, c-Myc activates the transcriptional activity of YTHDF1, promoting cancer cell proliferation and increasing chemosensitivity [41]. However, univariate and multivariate Cox regression analyses have clarified that YTHDF1 is a negative prognostic factor for colon cancer [42]. Studies revealed lower expression in the high-risk cancer group, indicating good value for predicting prognosis. Further studies implied that YTHDF1 identifies the m^{6}A-modified *ANKLE1* transcript, a tumor suppressor in CRC [106], indicating that YTHDF1 may be required for ANKLE1-regulated CRC inhibition and prevention. Similar to YTHDF1, YTHDC2 contributes to colon cancer metastasis by promoting *HIF-1α* translation, suggesting that YTHDC2 is a potential biomarker for diagnosis and treatment response evaluation for colon cancer patients [107].

In CRC, YTHDF3 was identified as a novel target of YAP signaling, by which YTHDF3 selectively binds to m^{6}A-modified *GAS5* to promote its decay and triggers CRC proliferation and metastasis [92]. Unlike that of other YTH domain proteins, the expression of YTHDF2 was unaffected in CRC tissues compared to nontumor tissues. Nonetheless, the binding of YTHDF2 to *SOX4* mRNA can be increased to induce the degradation of *SOX4*, indicating another view of the regulation and impact of m^{6}A on CRC [73]. Another study shows that high expression of METTL3 promotes m^{6}A-modified *SOX2* mRNAs, which is subsequently recognized by IGF2BP2 and leads to inhibition of *SOX2* mRNA degradation [105]. Although these observations provide the significant signatures of YTH domain proteins in CRC progression, more details and the related mechanisms need to be uncovered.

Table 1
Functional characterization of YTH domain-containing proteins in cancers.

m^6A readers	Cancer	Expression	Targets and Mechanism	Role	Reference
YTHDF1	Breast cancer	Upregulated	Not mentioned.	Positive prognostic signature	[37]
		Upregulated	Positive associated with *CDK1, MKI67, VEGFA.*	Positive prognostic signature	[38]
	Colorectal cancer	Upregulated	Enhances *TCF7L2* translation.	Oncogene	[39]
		Upregulated	Increases Wnt/β-catenin activity.	Oncogene	[40]
		Upregulated	Not mentioned.	Oncogene	[41]
		Downregulated	Not mentioned.	Negative prognostic signature	[42]
		Unknown	Facilitates *ANKLE1* expression.	Tumor suppressor	[43]
	Gastric cancer	Unaffected	Not mentioned.	Tumor suppressive signature	[44]
		Upregulated	Not mentioned.	Positive prognostic signature	[45]
	Hepatocellular carcinoma	Upregulated	Not mentioned.	Oncogene	[46]
		Upregulated	Not mentioned.	Oncogene	[47]
		Upregulated	Promotes translation of *Snail.*	Oncogene	[48]
		Upregulated	Promotes *FZD5* mRNA translation.	Oncogene	[49]
		Unknown	Increases the stability of *FOXO3* mRNA.	Oncogene	[50]
	Lung cancer	Upregulated	Promotes *YAP* mRNA translation.	Oncogene	[51,52]
		Upregulated	Promotes *PRPF6* mRNA expression.	Oncogene	[53]
		Upregulated	Targets *CDKs* and *Keap1-Nrf2-AKR1C1* axis	Dual effect	[54]
		Upregulated		Positive prognostic signature	[55]
		Upregulated in tumors but downregulated in higher pathological stages	Not mentioned.	Dual effect	[56]
		Upregulated	Disrupts the Wnt/b-catenin pathway.	Positive therapeutic target	[57]
	Melanoma	Unknown	Promotes *HINT2* translation.	Oncogene	[58]
		Upregulated	Interactes with *CDK1/2.*	Positive therapeutic target	[59]
	Ovarian cancer	Upregulated	Augments *EIF3C* translation.	Oncogene	[60]
		Unaffected	Promotes *TRIM29* translation.	Oncogene	[61]
	Cervical cancer	Unknown	Induces *PDK4* expression.	Positive therapeutic target	[62]
		Upregulated	Enhances *HK2* stability.	Positive therapeutic target	[63]
	Squamous cell carcinoma	Upregulated	Not mentioned.	Positive prognostic signature	[64]
		Upregulated	Promotes *c-Myc* stability.	Oncogene	[65]
		Upregulated	Enhances *TFRC* expression.	Positive therapeutic target	[66]
	Merkel Cell Carcinoma	Upregulated	Activates *eIF3* translation.	Oncogene	[67]
	Abdominal aortic aneurysm	Upregulated	Not mentioned.	Unknown	[68]
	Glioma	Upregulated	Not mentioned.	Positive prognostic signature	[69]
		Upregulated	Not mentioned.	Positive prognostic signature	[70]
YTHDF2	Bladder cancer	Upregulated	Promotes *SETD7, KLF4* degradation.	Oncogene	[71]
	Cervical cancer	Unknown	Mediates *GAS5* RNA degradation.	Potential therapeutic target	[72]
	Colorectal cancer	Unaffected	Promotes *SOX4* mRNA degradation.	Potential therapeutic target	[73]
	Gastric cancer	Downregulated	Promotes *FOXC2* degradation.	Negative prognostic signature	[74]
	Glioblastoma	Upregulated	Stabilizes *MYC, VEGFA* transcripts.	Potential therapeutic target	[75]
		Upregulated	Positively correlated with PD-1, TIM-3 and CTLA-4.	Positive prognostic signature	[76]
		Upregulated	Facilitates *LXRA, HIVEP2* mRNA decay.	Potential prognostic signature	[77]
	Hepatocellular carcinoma	Downregulated	Proceses *IL11, SERPINE2* mRNA dacay.	Pptential therapeutic target	[78]
		Downregulated	Destabilizing *EGFR* mRNA.	Tumor suppressor	[79]
		Unknown	Mediates *SOCS2* mRNA degradation.	Potential therapeutic target	[80]
		Upregulated	Not mentioned.	Positive prognostic signature	[81]
		Upregulated	Increases *OCT4* translation.	Potential therapeutic target	[82]
	Acute myeloid leukemia	Upregulated	Destabilizes *TNFRSF1B* mRNA.	Potential therapeutic target	[83]
		Unknown	Reduces *PFKP, LDHB* expression.	Negative prognostic signature	[84]
	Lung cancer	Upregulated	Facilitates *6PGD* mRNA translation.	Potential prognostic signature	[85]
	Ovarian cancer	Upregulated	Inversely correlated with miR-145.	Positive therapeutic target	[86]
	Pancreatic cancer	Unknown	Promotes *PER1* mRNA degradation.	Potential diagnostic and therapeutic target	[87]
	Prostate cancer	Upregulated	Facilitates *MOB3B* mRNA degradation.	Potential therapeutic target	[88]
		Upregulated	Not mentioned.	Positive therapeutic target	[89]
		Upregulated	Induces *LHPP, NKX3-1* mRNA degradation.	Potential diagnostic and therapeutic target	[90]
YTHDF3	Breast cancer	Upregulated	Positive associated with *CDK1, MKI67, VEGFA.*	Positive prognostic signature	[38]
		Upregulated	Induces *ST6GALNAC5, GJA1* translation.	Potential prognostic signature	[91]
	Colorectal cancer	Upregulated	Facilitates *GAS5* degradation.	Potential prognostic signature	[92]
	Hepatocellular carcinoma	Unknown	Enhancing *Zeb1* mRNA stability.	Potential therapeutic target	[93]
YTHDC1	Colorectal cancer	Upregulated	Not mentioned.	Positive therapeutic target	[94]
	Glioblastoma	Unaffected	Promotes *SRSF* decay.	Potential therapeutic target	[95]

(*continued on next page*)

Table 1 (*continued*)

m^{6}A readers	Cancer	Expression	Targets and Mechanism	Role	Reference
	Hepatocellular carcinoma	Upregulated	Not mentioned.	Positive prognostic target	[96]
	Prostate cancer	Unknown	Mediates *Cd44v5-Luc* splicing.	Positive therapeutic target	[97]
YTHDC2	Colon cancer	Upregulated	Promotes translation of *HIF-1α* and *Twist1*.	Potential prognostic signature	[98]
	Lung adenocarcinoma	Downregulated	Promotes *SLC7A11* mRNA decay.	Negative prognostic signature	[99]
		Downregulated	Not mentioned.	Negative prognostic signature	[100]
IGF2BPs	Breast cancer	Unknown	Promotes *CERS6* mRNA stability.	Potential therapeutic signature	[101]
	Gastric cancer	Upregulated	Promotes *HDGF* mRNA stability.	Potential prognostic biomarker	[102]
	Lung cancer	Upregulated	Not mentioned.	Positive prognostic signature	[103]
		Unknown	Enhances *VANGL1* mRNA stability.	Potential therapeutic target	[104]
	Colorectal cancer	Upregulated	Prevents *SOX2* mRNA degradation.	Potential biomarker	[105]

7. YTH proteins in liver cancer

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer [108]. The high prevalence of HCC has long been attributed to chronic viral hepatitis, while other risk factors, particularly genetic or epigenetic susceptibility, are gaining importance. Studies have shown that HCC is highly associated with abnormal m^{6}A deposition [80,109]. Interestingly, m^{6}A modification in these studies showed quite different effects on HCC progression: METTL3 promoted HCC via m^{6}A modification, but METTL14 was an adverse prognostic factor in HCC patients. Thus, the final outcome of m^{6}A modification in HCC could be determined by assessing m^{6}A-containing mRNAs and their readers.

Recently, a correlation analysis using the TCGA database showed that YTHDF1 is significantly overexpressed in HCC and positively associated with pathology stage, implying that YTHDF1 is a potential new therapeutic and prognostic marker in HCC [46]. Another similar study revealed the independent predictive value of both YTHDF1 and METTL3 for HCC patient overall survival [47]. In addition, in vitro and in vivo evidence indicated that YTHDF1 induces the progression of migration, invasion and epithelial-mesenchymal transition (EMT) in HCC cells by regulating *Snail* mRNA translation [48]. In addition, Wnt receptor-*FZD5* is another YTHDF1 target at the translational level in HCC. YTHDF1 promotes HCC cell proliferation and metastasis by accelerating the translational output of *FZD5* mRNA in an m^{6}A-dependent manner [49]. For HCC therapy, resistance to sorafenib (a first-line treatment for advanced HCC) remains a problem in developing individual therapeutic strategies. YTHDF1 was demonstrated to have an important role in modifying the hypoxic tumor environment by identifying *FOXO3* mRNA. This study validated that METTL3 mediates and that YTHDF1 recognizes *FOXO3* methylation, leading to inhibition of the autophagy signaling pathway to maintain sorafenib sensitivity in HCC [110]. Therefore, YTHDF1 may act as an oncogene and has the potential to serve as a positive molecular biomarker for evaluating the prognosis and treatment response of HCC patients. As a synergy factor of YTHDF1 in protein synthesis, YTHDF3 enhances the stability and lifetime of m^{6}A-methylated *Zeb1* mRNA. Upregulated *Zeb1* mediates circ_KIAA1429 expression, leading to a robust driving force for HCC migration, invasion and EMT [93].

However, the performance of YTHDF2 in HCC is more complicated, as shown above. YTHDF2 can work as both a molecular 'rheostat' and an 'accelerator', which depends on the mRNAs it processes. When its binds to *interleukin 11 (IL11)/serpin family E member 2 (SERPINE2)* or *EGFR*, YTHDF2 may act as a tumor suppressor [78,79]. In contrast, when YTHDF2 recognizes *OCT4* mRNA, it promotes HCC development and cancer metastasis [82]. In addition, there are several other studies showing that YTHDF2 has the potential to participate in HCC-related phenotypes, such as proliferation and migration [80] and immune cell infiltration [81], but further exploration is needed to determine the specific regulatory mechanisms.

8. YTH proteins in lung cancer

Lung cancer is a molecularly heterogeneous disease [111]. Understanding the molecular biology of lung cancer is helpful for finding promising strategies for early prognosis and treatment. Lung cancer is classified into two types: NSCLC and small-cell lung cancer (SCLC). NSCLC is the most common type, of which lung adenocarcinoma (LUAD) is the most common subtype. Recently, METTL3 was identified as a potential therapeutic target for patients with lung cancer as it promotes the translation of oncogenes [112,113]. The functions of m^{6}A readers in lung cancer remain largely unknown; the possible functions are discussed below.

The YAP signaling pathway plays a critical role in lung cancer, including in tumorigenesis, aggressiveness, metastasis, and resistance to drug treatment [114]. As a central component of the YAP signaling pathway, YTHDF1 is recruited to m^{6}A-modified YAP mRNA, inducing NSCLC drug resistance and metastasis by promoting YAP translation [51,52]. Another m^{6}A target, *PRPF6,* screened by LUAD TCGA dataset analysis, was shown to be positively expressed with YTHDF1. In this study, the authors found that YTHDF1-dependent *PRPF6* m^{6}A methylation is a key regulator of ATTM-induced anticancer effects. The mechanism mediated by the m^{6}A-*PRPF6*-YTHDF1 axis indicates an opportunity for overcoming the side effects caused by ATTM therapy by scavenging H2S [53]. Consistently, according to different datasets from the TCGA and Gene Expression Omnibus (GEO), YTHDF1 is overexpressed in LUAD patients versus normal controls [115]. In addition, YTHDF1, together with 5 other m^{6}A-related genes, was screened to build a risk scoring signature that was strongly related to pathological stage, sex and overall survival, indicating that YTHDF1 has good predictive value in LAUD [56]. Additionally, m^{6}A modification was found to participate in lung cancer cell metabolism via its reader YTHDF2 [85]. In this study, upregulated YTHDF2 bound to *6-phosphogluconate dehydrogenase (6PGD)* and promoted *6PGD* mRNA translation, indicating that YTHDF2 is a lung cancer promoter. IGF2BPs are also detected abnormally upregulated in LAUD tissue [103]. After irradiation, m^{6}A level of *VANGL1* is upregulated, as well as the *VANGL1* mRNA stability regulated by IGF2BP2/3, suggesting a regulatory role of IGF2BPs in LUAD radio resistance [104].

Resistance to hypoxia-induced apoptosis, leading to distinctive hypoxia adaption in de novo lung adenocarcinomas (ADCs), has been an inevitable barrier leading to poor clinical outcomes of NSCLC treatment. The search for more specific hallmarks and treatments in both ADC and hypoxia-adapted NSCLC has become necessary and urgent. In the two different progressions of NSCLC, YTHDF1 behaves in completely distinct manners and provides us with new insights into cancer biology [54]. In ADC, YTHDF1 deficiency impedes cancer progression by inhibiting NSCLC cell proliferation and xenograft tumor formation through regulating the translation activity of cyclin proteins. However, lower expression of YTHDF1 is correlated with a worse clinical outcome

because of the resistance to cisplatin treatment in cancerous cells. Depletion of YTHDF1 in hypoxic solid tumors makes cancerous cells more resistant to cisplatin-dependent chemotherapy by regulating the *Keap1-Nrf2-AKR1C1* axis. In contrast, YTHDC2 is frequently suppressed in LUAD [99,100]. Mouse model studies have shown that YTHDC2 preferentially binds to *SLC7A11* mRNA and decreases tumorigenesis by suppressing cystine uptake and blocking the downstream antioxidant program [99].

9. YTH proteins in other cancers

The mRNAs recognized by YTH domain-containing proteins largely determine their roles in the progression of specific cancers. In oral squamous cell carcinoma, *c-Myc* is a direct YTHDF1 target gene and is responsible for the acceleration of tumor growth [65]. The negative p53 regulators *YY1* and *MDM2* are targets stimulated by YTHDF2 to promote human keratinocyte transformation in arsenic carcinogenesis [116]. In ocular melanoma, YTHDF1 inhibits the progression of both uveal and

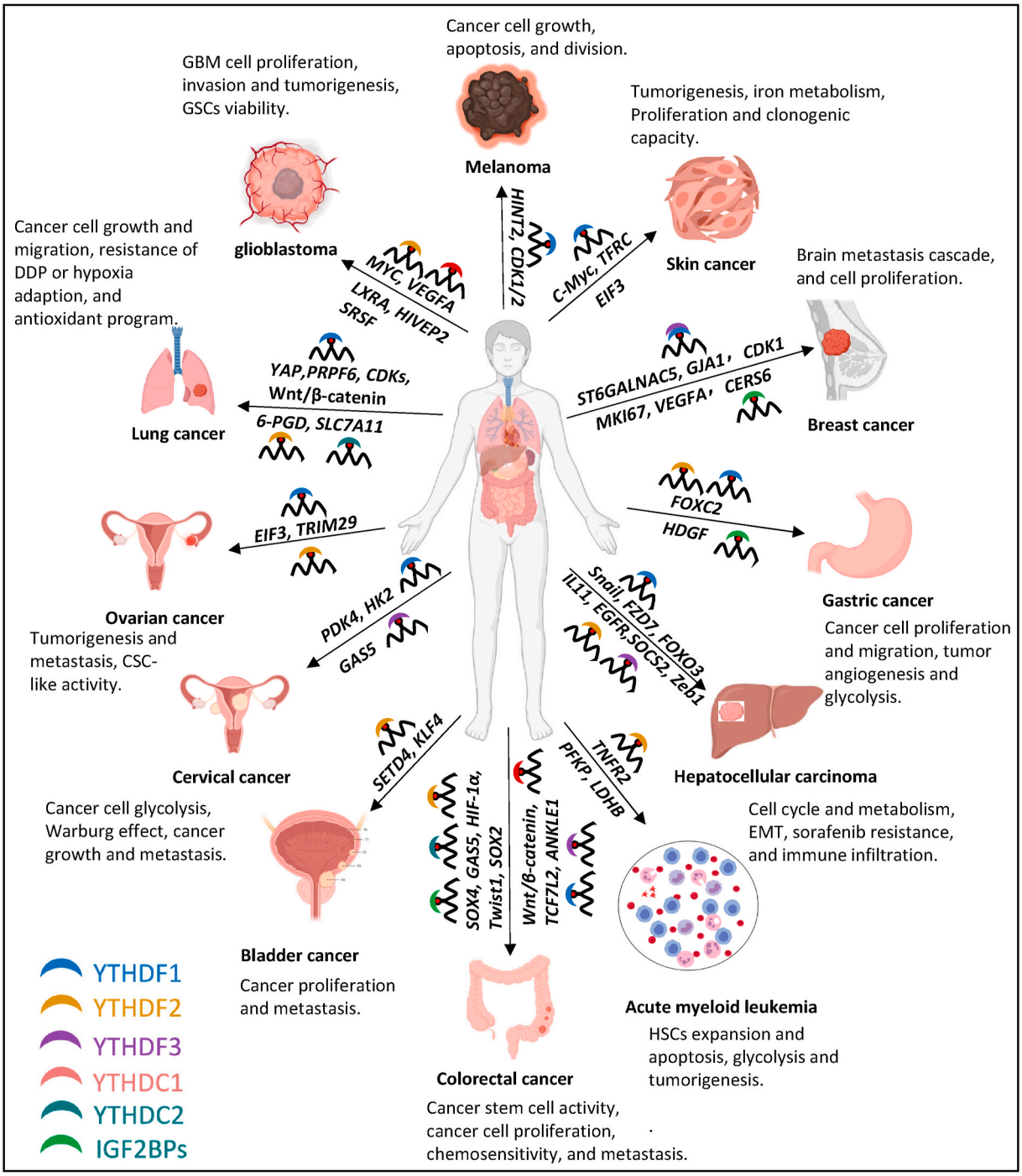

Fig. 3. Deregulation of m^{6}A reader proteins in human cancers.
A comprehensive overview of m^{6}A readers in human carcinogenesis, including proliferation, migration, invasion, metastasis, and chemoresistance regulation. These readers specifically identify m^{6}A-modified mRNAs and subsequently regulate critical signaling pathways in the pathogenesis of cancers. Red box line indicates upregulated expression and oncogenic functions. Blue line indicates downregulated expression and tumor suppresive functions. Black line indicates contradicted roles within different studies. Dashed gray line indicates unaffected or unknown roles.

conjunctival melanoma by promoting the translation of the tumor suppressor *HINT2* [58]. Notably, in addition to being recognized by YTHDF3 in CRC, the tumor suppressor *GAS* is also identified by YTHDF2 in cervical cancer and acts as a critical molecule for cervical cancer progression [72]. YTHDF2 also binds to *FOXC2, TNFRSF1B, PER1*, and *MOB3B* in gastric cancer, AML, pancreatic cancer and prostate cancer, respectively, providing similar insights into the underlying mechanisms of carcinogenesis induced by RNA degradation [74,83,87,88]. In glioblastoma (GBM), despite different target transcripts, YTHDF1/2 and YTHDC1 display similar function on GBM growth and progression, indicating positive prognostic and therapeutic prospects of these readers [69,70,75–77,95].

Studies have also indicated that more than one individual transcript participates in m^{6}A reader-mediated effects in cancers. In ovarian cancer and Merkel cell carcinoma, YTHDF1 augments m^{6}A-modified *EIF3C* translation and concomitantly increases the global translational output, thus facilitating tumorigenesis and cancer metastasis [60,67]. Additionally, YTHDF1 has been verified to bind to m^{6}A-modified *PDK4* or *HK2* and promote cancer cell metabolic processes, such as glycolysis or the Warburg effect in cervical cancer, which suggests that YTHDF1 could be a promising therapeutic target [62,63]. Similarly, a group of transcripts encoding lysosomal proteases in dendritic cells are methylated and then recognized by YTHDF1. Deletion of YTHDF1 markedly inhibits these cathepsins, thus enhancing the antitumor response of antigen-specific CD8$^+$ T cells [117]. In bladder cancer, *SETD7* and *KLF4* were both identified as direct targets of YTHDF2 through transcriptome sequencing and confirmed with methylated RNA immunoprecipitation (MeRIP)-RT-qPCR [71].

In addition, other studies have indicated a positive correlation between YTHDF1 expression and cancer development, but there is a lack of mechanistic evidence in abdominal aortic aneurysm [118] and head and neck squamous cell carcinoma [119]. Likewise, low expression of YTHDC2 is significantly associated with worse overall survival in lung cancer patients. However, the potential RNAs that interact with YTHDC2 still need to be explored [100]. Further research is required to decipher the specific targets of m^{6}A readers in these cancers, which may contribute to the understanding of their clinical significance and potential applications.

10. Conclusions and future perspectives

In this review, we summarized nearly all the recent findings on YTH domain-containing proteins in cancers. Dysregulation of m^{6}A readers in cancer tissues results in abnormal mRNA metabolism of oncogenes and tumor suppressors, leading to the acceleration or delay of cancer development (Fig. 3). However, our understanding of how YTH proteins contribute to these processes remains incomplete. It is essential to identify the intrinsic and extrinsic signals that regulate the recruitment of YTH proteins to m^{6}A-modified mRNAs and to identify these transcripts in a specific biological environment. In addition, the mechanisms that control the expression and activities of YTH proteins remain largely unknown. Therefore, future elucidation of the accurate roles of YTH proteins in regulating gene expression in cancers with new tools and methods is needed.

The crucial role of m^{6}A readers in cancer initiation and progression provides potential targets for the treatment of cancers. Indeed, inhibition of YTHDF1 showed therapeutic potential alone or in combination with anti-PD-L1 immunotherapy in CRC [39,117]. However, small-molecule agents targeting YTH proteins, by blocking their interaction with m^{6}A-modified mRNAs or other regulatory proteins, remain to be identified or developed. These small molecules might serve as a potential way to inhibit dysregulated mRNA metabolism by YTH proteins in cancer. On the other hand, targeted m^{6}A editors and readers based on CRISPR/dCas system have been recently developed [30–33]. Taking advantage of these tools, manipulating the oncogenic or tumor suppressive mRNAs of interest with specific editors or readers could be achieved to modulate cancer cell characteristics. Of note, Li et al. have used dCas13b-ALKBH5 to demethylate m^{6}A modifications on oncogene transcripts such as *EGFR* and *MYC*, resulting in altered cancer cell proliferation in vitro [31]. However, whether these tools could be applied to cancer treatment remains to be explored.

Author contributions

All the authors summerized and discussed. B.H. and X.G. wrote the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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