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REVIEW ARTICLE

The role of regulators of RNA m^{6}A methylation in lung cancer

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Abstract N^6-methyladenosine (m^{6}A) modification is found the most prevalent and abundant post-transcriptional mRNA modification in eukaryotic cells. It regulates almost all stages of RNA life cycle including splicing, translocation, stability, decay and translation. As a dynamic and reversible process, m^{6}A modification is catalyzed by the RNA methyltransferases ('writers'), removed by the demethylases ('erasers'), and interacts with m^{6}A-binding proteins ('readers'). Recent studies have revealed that these m^{6}A modification regulators are frequently expressed aberrantly in various types of cancer, and involved in cell proliferation, differentiation, metabolism, particularly, in tumorigenesis and tumor progression through diverse mechanisms. In this review, the m^{6}A modification process and its regulatory functions in lung cancer are summarized. Furthermore, the research progress in the inhibitor development of m^{6}A modification, and the potential of targeting m^{6}A modifying proteins for clinical application are discussed.

Introduction

Lung cancer is the most common cancer in the world (~11.6% of total cases), with the highest mortality (18.4% of all cancer deaths). Lung cancer has become one of the most serious threats to human health.[1,2] According to the histological characteristics, lung cancer can be classified into two major subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Among them, NSCLC accounts for 80%–85% of total lung cancer cases. NSCLC can be further classified into three types: adenocarcinoma,

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squamous cell carcinoma and large cell carcinoma. The 5-year survival rate of NSCLC patients is only 15%. The occurrence and progression of lung cancer are complicated and consist of several steps. Understanding of molecular mechanisms of carcinogenesis, identification of biomarkers for diagnosis and prognosis, and the development of novel therapy strategies for lung cancer are urgently needed.

The post-transcriptional modifications have been proved to play critical roles in a variety of physiological and pathological processes. Among numerous types of RNA modifications, N^6-methyladenosine (m^6A), which was first identified in the 1970s,[3–5] is the most prevalent and abundant internal mRNA modification in eukaryotic cells.[6,7] Similar to the methylation modification in DNA, the m^6A RNA methylation regulates the post-transcriptional expression of genes without changing the base sequence. It has been found that m^6A mainly occurring within the "RRACH" consensus sequence (R = A or G, H = A, C, or U), which is enriched in the stop codon, 3' untranslated region (UTR) and long internal exon.[8–10]

Studies have revealed that m^6A modification participates in almost all stages of RNA life cycle including mRNA splicing, exportation, stabilization and translation.[11–14] Besides mRNA, the m^6A methylation also regulates the generation and function of ribosomal RNA (rRNA), transfer RNA (tRNA), and non-coding RNAs (ncRNA) including long non-coding RNA (lncRNA), microRNA (miRNA) and circular RNAs (circRNA). Recently, m^6A has been reported to be present on some special regulatory RNAs. Liu et al revealed that METTL3 may deposit m^6A modifications on chromosome-associated regulatory RNAs (carRNAs), such as enhancer RNAs, promoter-associated RNAs, and repeat RNAs. Depletion of METTL3 reduces m^6A modification and promotes open chromatin state and downstream RNA transcription.[15]

In nucleus, the m^6A modification of RNA is dynamically and reversibly regulated by two groups of catalytic proteins: the methyltransferases (also called "writers"), and the demethylases (also called "erasers").[16–18] A group of m^6A binding proteins (also called "readers") subsequently recognize and bind to the m^6A-rich domain in RNA, and perform corresponding downstream functional processes.

Numerous studies have demonstrated that aberrant m^6A methylation closely correlate with tumorigenesis and progression of human cancers through diverse mechanisms.[19–21] The dysregulations of writers, erasers and readers are proved to regulate these processes by activating oncogenes or inhibiting tumor suppressors.[22,23] Recent studies have also revealed that dysregulated m^6A methylation plays critical roles in lung cancer.[24,25] In this review, we summarized the latest research progress in the function and underlying mechanism of m^6A methylation in lung cancer, and discussed the potential of targeting m^6A modifying proteins for cancer therapy.

Regulators of RNA m^6A methylation

There are mainly 3 classes of m^6A methylation regulators: writers, erasers and readers. The cross-talks among them are involved in tumorigenesis and tumor progression (Fig. 1).

Writers

The identified m^6A writers consist of methyltransferase-like protein 3 (METTL3), METTL14, METTL16, METTL5 and their cofactors Wilms tumor 1associated protein (WTAP), RNA-binding motif protein 15 (RBM15/15B), Vir-like m6A methyltransferase associated (VIRMA; also known as KIAA1429), zinc finger CCCH-type containing 13 (ZC3H13) and Cbl proto-oncogene-like 1 (CBLL1; also known as HAKAI).

m^6A is introduced co-transcriptionally by the methyltransferase complex (MTC) which consists of METTL3 and other accessory components including METTL14, WTAP, RBM15, VIRMA and ZC3H13.[26] METTL3 is the first identified component of the m^6A MTC. It serves as the primary methyltransferase critical for m^6A methylation and is highly conserved in eukaryotic cells from yeast to human. METTL3 is a sadenosyl methionine (SAM)-binding protein which catalyzes the transfer of methyl groups in SAM to adenine bases in RNA and produces sadenosyl homocysteine (SAH). Aberrant expression of METTL3 affects the total level of m^6A methylation.[10,27]

METTL14 is another active component in the m^6A MTC. Studies have revealed that METTL3 and METTL14 are co-localized in nuclear speckles and form stable heterodimer.[28] In m^6A MTC, only METTL3 acts as a catalyst, whereas METTL14 primarily acts to form a stable structure with METTL3 and plays a key role in recognizing specific sequences in catalytic substrates.[28–30] METTL3-METTL14 heterodimer forms the core MTC inducing m^6A modification synergistically.

Similar to METTL14, WTAP has no methyltransferase activity. Its major function is to ensure the METTL3-METTL14 heterodimer could local to the nuclear speckle.[31,32] RBM15 and RBM15B also have no catalytic function. They bind to METTL3 and WTAP, and recruit the MTC to specific RNA sites for m^6A modification.[33,34] VIRMA/KIAA1429 mediates region-selective m^6A methylation of adenine bases in 3'UTR and near stop codon by recruiting the MTC, and also interacts with cleavage and polyadenylation specificity factor subunit 5 and 6 (CPSF5 and CPSF6).[35] ZC3H13 contains abundant low-complexity domains. By bridging WTAP to the mRNA-binding factor Nito, ZC3H13 promotes the m^6A MTC retained in nuclear speckles and improves its catalytic function.[34,36] ZCCHC4, another CCHC zinc-finger-containing protein, is found to involve in the modification of the 28S rRNA, mediates rRNA ribosome subunit distribution and global translation.[37]

METTL16 is a newly discovered m^6A writer which possesses methyltransferase activity. Shima et al showed that METTL16 regulates mRNA stability and splicing, and the binding sites of METTL16 do not overlap with those of METTL3/METTL14 methylation complexes, suggesting its independent functions.[38] Pendleton et al found that METTL16 directly binds to pre-RNA and regulates the splicing of SAM synthetase.[39] In addition, METTL16 could function alone and catalyze U6-snRNA m^6A methylation on A43 box ("ACAGAGA") and regulate tumorigenesis by targeting pre-mRNAs and ncRNAs.[40]

Another new methyltransferase responsible for 18S rRNA m^6A modification, METTL5, is identified in 2019.[41,42] By forming a heterodimer with a co-activator TRMT112, the

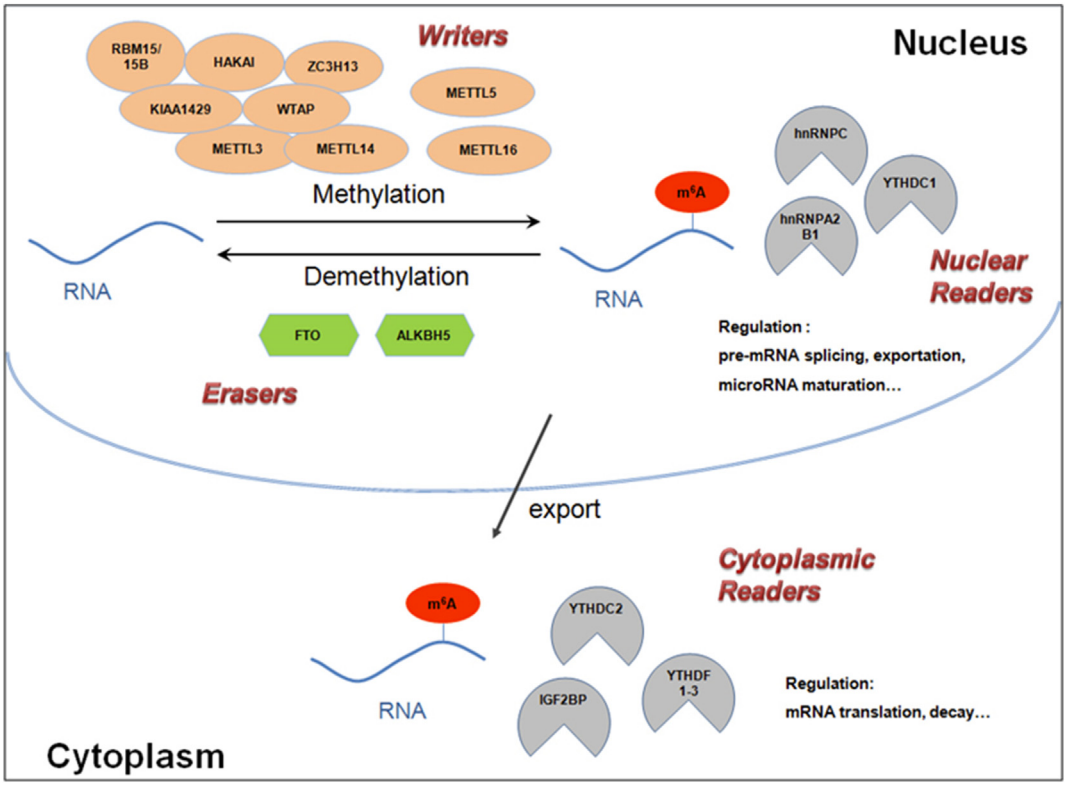

Figure 1 Mechanism of RNA m^{6}A modification.

metabolic stability of METTL5 and modification area on precursor and mature forms of 18S rRNA is increased. The structure of METTL5-TRMT112 heterodimer suggests its different RNA binding mode from other m^{6}A writers. Furthermore, co-immunoprecipitation studies revealed that there are more than 100 proteins may bind to METTL3 or METTL14,[43] suggesting there may be other components of the m^{6}A methyltransferase complexes exist.

Erasers

The demethylases can remove m^{6}A in RNA and called as 'erasers'. To date, there are only two m^{6}A erasers have been identified, the fat mass and obesity-associated protein (FTO) and the AlkB homolog 5 (ALKBH5). These two proteins are all belong to the alpha-ketoglutarate-dependent dioxygenase family and catalyze m^{6}A demethylation in a Fe (II) and α-ketoglutaric acid-dependent manner. However, the demethylases activities of them are independent of each other. These two proteins are mainly localized in the nucleus where the removal of m^{6}A mainly occurs. Whether there is any other m^{6}A demethylase located in the cytoplasm and how the m^{6}A is modified in the cytoplasm is still not clear.

FTO is the first molecule identified to catalyze m^{6}A demethylation, and highly expressed in muscle and brain. It mediates demethylation with its oxidative activity by targeting the m^{6}A-rich region in RNA.[44,45] Rau et al investigated the mechanism of sequence-specific m^{6}A demethylation of FTO by fusing FTO and RCas9 together as an RNA targeting module. This ingeniously designed RCas9-FTO retained the demethylation activity and bound to RNA in a sequence-specific manner depending on the single-guide RNA (sgRNA) and PAMmer.[46] The study of FTO function confirms that the m^{6}A modification is a dynamic and reversible process. Accumulating evidences show that FTO interacts with different RNA modifications, such as m^{6}A, m^{6}A$_m$, m^{1}A, 6 mA, 3 mT. Zhang et al investigated the role of FTO structure in FTO function in different RNA substrates. Their study showed that the catalytic activity of FTO depends on the interaction of residues in the catalytic pocket with the nucleobase, also depends on the sequence and the tertiary structure of RNA. They found that m^{6}A is the most favorable substrate of FTO.[47]

ALKBH5 is the second identified m^{6}A eraser and its expression is particularly abundant in the testes.[48] ALKBH5 catalyzes m^{6}A demethylation in RNA, also takes part in splicing and the formation of longer 3' UTR mRNAs.[49,50] Interestingly, the activity of ALKBH5 and FTO are similar but also specific. Zou et al illustrated that an m^{6}A-induced conformational change which is not in the consensus sequence (GG (m^{6}A)CU) in RNA may account for the specificity.[51] Furthermore, FTO could mediate m^{6}A$_m$ (N6, 2′-O-dimethyladenosine) demethylation while ALKBH5 is an m^{6}A-specific demethylase.[52] Recent studies reported that ALKBH3 is a novel m^{6}A eraser, and it preferentially modifies tRNA than mRNA or rRNA.[53]

Readers

For different downstream biological functions, the m^{6}A modification must be identified by interacting factors such

Table 1 Target genes, mechanisms and functions of m^{6}A regulators in lung cancer.

Regulator	Target	Molecular mechanism	Function	Refs
METTL3	*EGFR* and *TAZ*	Promotes the translation of *EGFR* and *TAZ*	Promotes growth, survival, and invasion of human lung cancer cells	24
METTL3	*eIF3h* and *BRD4*	Interacts with *eIF3h*, and promotes the translation of *BRD4*	METTL3-eIF3h interaction is required for enhanced translation, formation of densely packed polyribosomes and oncogenic transformation in human lung cancer cells.	68
METTL3	*YAP*	Promotes *YAP* translation via recruiting YTHDF1/3 and eIF3b to translation initiation complex, and increases YAP mRNA stability through regulating MALAT1-miR-1914-3p-YAP axis	Induces treatment resistance and metastasis in NSCLC cells.	69
METTL3	*ZBTB4*	Reduce the expression of *ZBTB4*	Promotes the cigarette smoke extract induced EMT in lung cancer cells	70
METTL3	*VASH1*	Promotes the biogenesis of miR-143−3p, and inhibits the expression of *VASH1*	Induces brain metastasis and angiogenesis of lung cancer cells	71
METTL3	*JUNB*	Enhances the mRNA stability of *JUNB*	Contributes to the TGF-β-induced EMT in lung cancer cells	72
METTL3	*lncRNA ABHD11-AS1*	Enhances the transcript stability and expression of *lncRNA ABHD11-AS1*	Promotes the proliferation and Warburg effect in NSCLC cells	73
METTL3	Bax/Bcl-2, PI3K/Akt pathway	Promotes PI3K/Akt signaling pathway	Knockdown of METTL3 inhibits the survival, proliferation and migration of NSCLC cells	74
METTL14	*NOTCH1*	Reduces the stability of *NOTCH1* mRNA, and regulates *NOTCH1* expression with GPER	GPER could promote NSCLC cell growth via regulating the YAP1/circNOTCH1/m6A methylated NOTCH1 pathway	76
FTO	*MZF1*	Increases the mRNA stability of *MZF1*, leading to enhanced MZF1 expression	Facilitates the proliferation, invasion and the malignant phenotypes of lung squamous cells	77
FTO	*USP7*	Increases the mRNA stability of *USP7*	Promotes the proliferation and the colony formation ability of lung cancer cells	78
ALKBH5	*FOXM1*	Increases the translation efficiency of *FOXM1* mRNA, and promote the expression	Promotes the proliferation and invasion of lung adenocarcinoma cells under intermittent hypoxia (IH) conditions	79
ALKBH5	*UBE2C*	Increases the mRNA stability of *UBE2C* and promotes the expression	Represses autophagy and aggravates cell proliferation, colonigenicity and invasive growth of NSCLC	80
ALKBH5	*YAP*	Reduces YTHDFs-mediated *YAP* expression and inhibits miR-107/LATS2-mediated YAP activity	Inhibits cellular proliferation, invasion, migration, and EMT of NSCLC cells *in vitro* and inhibits tumor growth and metastasis *in vivo*	81
YTHDF2	*6PGD*	Promotes the translation of *6PGD* mRNA and enhances the PPP	Promotes the growth of lung cancer cells	82
IGF2BP1	*SRF*	Increases the stability of *SRF* mRNA, and promotes the expression of SRF	Promotes the cell growth and invasion of lung cancer cells.	83
YTHDC2	*SLC7A11*	Reduces the stability of *SLC7A11* mRNA	Decreases tumorigenesis and exhibits antitumor activity in human LUAD	84
YTHDC2	*CYLD*	Inhibits the degradation of *CYLD* mRNA and promotes the expression of *CYLD*, then inhibits the NF-κB pathway activity	Promotes the proliferation and migration of lung cancer cells	85

Abbreviations: ALKBH5: AlkB homolog 5; BRD4: bromodomain-containing protein 4; CYLD: cylindromatosis; EGFR: epidermal growth factor receptor; eIF3h: eukaryotic translation initiation factor 3h; EMT: epithelial−mesenchymal transition; FOXM1: forkhead box M1;

FTO: fat mass and obesity-associated protein; GPER: G protein-couples oestrogen receptor; IGF2BPs: insulin-like growth factor 2 mRNA-binding proteins; LATS2: large tumor suppressor kinase 2; LUAD: human lung adenocarcinoma; MALAT 1: metastasis associated in lung adenocarcinoma transcript 1; METTL3: methyltransferase-like protein 3; METTL14: methyltransferase-like protein 14; MZF1: myeloid zinc finger 1; NSCLC: non-small cell lung cancer; PPP: pentose phosphate pathway; SRF: serum response factor; TAZ: tafazzin; TGF-β: transforming growth factor-β; UBE2C: ubiquitin-conjugating enzyme E2C; USP7: ubiquitin specific protease 7; VASH1: vasohibin-1; YAP: yes associated protein; YTHDC: YTH domain-containing proteins; YTHDF: YTH-family proteins; ZBTB4: Zinc finger and BTB domain-containing 4; 6PGD: 6-phosphogluconate dehydrogenase.

as YTH domain-containing proteins (YTHDC1-2), YTH-family proteins (YTHDF1-3), heterogeneous nuclear ribonucleoproteins (including hnRNPC, hnRNPG and hnRNPA2B1) and insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs). These proteins are defined as 'reader'.

The YT521-B homology (YTH) domain family members, including YTH domain family proteins (YTHDF1-3) and YTH domain containing proteins (YTHDC1-2), are the most important readers and have conserved m^{6}A binding domains.[54] In cytoplasm, YTHDF1-3 proteins work synergistically to influence RNA metabolism.[45,54,55] YTHDF2 is the first identified m^{6}A reader. It selectively binds to m^{6}A modified mRNA and regulates RNA degradation. The C-terminal region of YTHDF2 recognizes specific m^{6}A sites, and the N-terminal region binds to the SH domain of CCR4-NOT transcription complex subunit 1 (CNOT1), thus it could recruit the CCR4-NOT deadenylase complex and transport RNA to the processing body (P-body) to accelerate the degradation of m^{6}A modified RNA.[56] Different to YTHDF2, YTHDF1 binds to m^{6}A sites close to stop codon in mRNA, and recruits the translation initiation complex (including eIF3, eIF4E, poly(A) binding protein (PABP)) and the 40S ribosomal subunit to promote translation of target RNA.[45] YTHDF3 promotes RNA translation by cooperating with YTHDF1 and initiation factor eIF4A3, and mediates mRNA decay through direct interaction with YTHDF2.[54,55,57]

The main role of YTHDC1 is to regulate mRNA export. YTHDC1 exports m^{6}A-containing mRNA from the nucleus to the cytoplasm through interacting with serine- and arginine-rich splicing factor 3 (SRSF3) and the splicing factor. When YTHDC1 is repressed, methylated mRNAs are accumulated in the nucleus.[58] Lesbirel et al reported that YTHDC1 plays a synergistic role with the three prime repair exonuclease (TREX) mRNA export complex by interacting with SRSF3, and promotes the exportation of m^{6}A methylated mRNA from the nucleus to cytoplasm.[59] YTHDC1 also participates in the regulation of m^{6}A methylation by regulating intracellular SAM synthesis.[38] YTHDC2 enhances the translation efficiency of target mRNA. Studies have shown that YTHDC2 knockdown causes the upregulation of the m^{6}A-modified transcripts, and this function of YTHDC2 is essential for fertility in mammals.[60,61]

The proteins of hnRNPs superfamily related to m^{6}A modification consist of HNRNPA2B1, HNRNPC and HNRNPG. HNRNPA2B1 participates in primary RNA (pri-miRNA) processing and alternative splicing by interacting with drosha ribonuclease III (DROSHA) and DiGeorge syndrome critical region 8 (DGCR8)[62]; whereas HNRNPC and HNRNPG selectively recognize m^{6}A-induced mRNA secondary structures and regulate mRNA abundance and splicing.[63,64]

IGF2BP1/2/3 (insulin-like growth factor 2 mRNA-binding proteins 1, 2, and 3) is a new class of m^{6}A reader. Different to the functions of YTHDF2, IGF2BPs enhance the stability and translation of their target mRNAs by recognizing the consensus GG (m^{6}A)C sequence under normal and stressed conditions.[65]

Notably, because the interactions between m^{6}A modifications and RNA-binding proteins are complicated, mRNA expressions are regulated at multiple levels.

Regulators of RNA m^{6}A methylation in lung cancer

m^{6}A methylation regulates RNA processing and metabolism and participates in carcinogenesis. On one hand, m^{6}A-modification itself may lead to alterations of mRNA translation, acts oncogenic role and accelerate tumor progression. On the other hand, the dysregulation of m^{6}A writers, erasers and readers also facilitates tumor development.[21] Several studies also showed that m^{6}A regulators influence the prognosis of lung cancer patients.[66,67]

Writers

m^{6}A writers deposit m^{6}A on mRNA and non-coding RNAs, regulates the expression of oncogene and tumor suppressor gene, and play critical role in lung cancer initiation and progression.

Numerous studies showed that METTL3 acts as an oncogene in lung cancer; it promotes lung cancer progression via diverse mechanisms. (a) Regulation on gene translation. METTL3 stimulates the translation of *epidermal growth factor receptor (EGFR)* and *tafazzin (TAZ)*, promotes the growth, survival and invasion of lung cancer cells.[24] By direct interaction with the eukaryotic translation initiation factor 3 subunit h (eIF3h), METTL3 promotes translation of many oncogenic mRNAs such as bromodomain-containing protein 4 (BRD4).[68] Jin et al reported that METTL3 promotes *yes-associated protein (YAP)* translation and increases YAP activity which leads to NSCLC drug resistance and metastasis.[69] Studies also demonstrate that METTL3 may repress gene expression in lung cancer cells. In cigarette smoke extract (CSE) treated human bronchial epithelial (HBE) cells, METTL3 level is elevated. METTL3 introduces m^{6}A modification to *Zinc finger and BTB domain-containing 4 (ZBTB4)* to reduce *ZBTB4* expression, which is responsible to CSE induced epithelial—mesenchymal transition (EMT) in lung cancer cells.[70] (b) Regulation on miRNA biogenesis. METTL3 increases the splicing of precursor miR-143—3p to stimulate its biogenesis. Increased miR-143—3p accelerates bone metastasis of lung cancer by targeting vasohibin-1 (VASH1).[71] (c) Regulation on mRNA and lncRNA stability. METTL3 enhances the mRNA stability of *JUNB*, a transcriptional regulator of EMT, and contributes to TGF-β induced EMT in lung cancer cells.[72] LncRNA ABHD11-AS1 is upregulated in NSCLC cells; it

stimulates the proliferation and Warburg effect of NSCLC cells. Further study illustrates that METTL3 enhances the transcript stability of *ABHD11-AS1* to increase its expression.[73] (d) Regulation on signaling pathway. MiR-600 inhibits migration and proliferation of lung cancer cells. The mechanistic study revealed that miR-600 targets METTL3. The reduced METTL3 alters the expression and phosphorylation of members of PI3K/Akt signaling pathway.[74]

Interestingly, METTL3 itself is also modulated in lung cancer which affects its function. Du et al reported that METTL3 is SUMOylated at lysine residues K177, K211, K212 and K215. The SUMOylation represses METTL3 activity and reduces the m^{6}A level of mRNA, resulting in enhanced tumor growth.[75]

For the role of other m^{6}A writers in lung cancer, Shen et al reported that METTL14 modulates m^{6}A level of *NOTCH1* mRNA, increases the translation level of *NOTCH1* and promotes NSCLC cell growth.[76]

Erasers

m^{6}A erasers are involved in lung cancer through regulating m^{6}A levels and mRNA stability of certain genes. FTO is identified as a prognostic factor in lung squamous cell carcinoma (LUSC). It facilitates proliferation and development of LUSC cells by decreasing the m^{6}A levels in *myeloid zinc finger 1 (MZF1)* mRNA and enhancing its stability.[77] In addition, Li et al revealed that high level of FTO promotes proliferation and colony formation of NSCLC cells by improving *ubiquitin-specific peptidase 7 (USP7)* mRNA stability and expression.[78]

ALKBH5 is another m^{6}A eraser, it was found to promote the proliferation and invasion of lung adenocarcinoma cells under intermittent hypoxia (IH) conditions by down-regulating m^{6}A modification of *forkhead box M1 (FOXM1)* mRNA and promoting *FOXM1* expression.[79] In NSCLC, upregulated ALKBH5 decreases the m^{6}A level and promotes the expression of *ubiquitin-conjugating enzyme E2C (UBE2C)* leading to NSCLC progression.[80] Although several studies demonstrated that ALKBH5 promotes lung cancer progression, ALKBH5 is also reported to suppress lung cancer. Jin et al revealed that ALKBH5 inhibits tumor growth and metastasis of NSCLC by reducing YTHDFs mediated YAP expression and inhibiting YAP activity.[81] The opposite roles of ALKBH5 reported in lung cancer by different groups maybe due to the cell and animal models, the pathological stages, and study methods. Further investigation is needed to explore the complicity of lung cancer.

Readers

m^{6}A readers play opposite roles in lung cancer. YTHDF2 was found up-regulated and promotes proliferation in lung cancer cells. By directly binding to the m^{6}A-modified site in 6-phosphogluconate dehydrogenase (6-PGD), YTHDF2 promotes the translation of 6PGD mRNA and enhances the pentose phosphate pathway (PPP).[82] IGF2BP1 promotes growth and invasion of lung cancer cells and associated with poor prognosis by impairing the miRNA directed decay of the serum response factor (SRF) mRNA.[83] In contrast, readers also act as tumor suppressors. YTHDC2 inhibits lung adenocarcinoma tumorigenesis by suppressing cystine uptake and blocking downstream SLC7A11-dependent antioxidant program.[84] Wang et al revealed that YTHDC2 was down-regulated in lung cancer. The overexpression of YTHDC2 inhibited the proliferation of lung cancer cells as well as tumor growth in nude mice. The mechanistic study showed that cylindromatosis (CYLD)/NF-κB pathways mediated YTHDC2's inhibitory effect.[85]

So far, most m^{6}A modifications in lung cancer were found on mRNA, miRNA and lncRNA. Interestingly, recent study reported that in mouse embryonic stem cells, METTL3 introduces m^{6}A modifications to regulatory RNAs such as enhancer RNAs, repeat RNAs. Since enhancer RNAs play important roles in cancer,[86] whether m^{6}A modification on enhancer RNAs is involved in lung cancer warrants further investigation.

The target genes, potential mechanisms and functions of related m^{6}A regulators in lung cancer are summarized in Table 1.

Gene expression profiles of m^{6}A methylation regulator for diagnosis and prognosis

The dysregulated expression of m^{6}A regulators can be used for potential clinical purpose. Li et al study showed that the expression of 19 m^{6}A regulators was significantly different in lung cancer tissues, and identified a three-m^{6}A-regulator signature (KIAA1429, METTL3, and IGF2BP1) as an independent prognostic model for patient stratification, prognostic assessment, and personalized treatment.[87] Based on TCGA dataset analysis, Li et al found that a profile of ten m^{6}A-associated regulators is significantly related to advanced lung cancer stage, they also showed that the loss of FTO and YTHDC2 is associated with poor overall survival (OS) rate.[88] Shi et al reported that in NSCLC tissues, high level of YTHDF1 links to hypoxia adaptation and cancer progression.[89] Similar researches were conducted in lung adenocarcinoma, risk scoring signatures contain 3, 6, or 11 m^{6}A methylated genes were built for clinical diagnosis and prognosis by different research groups.[90–92] These studies suggest that m^{6}A regulators could be potential diagnostic markers for diagnosis and prognosis of lung cancer.

Therapeutic potential of targeting m^{6}A methylation regulators

Since it is proved that the m^{6}A methylation of RNA plays important roles in tumorigenesis and tumor progression, m^{6}A methylation regulators could serve as potential therapeutic targets for drug development.

Several FTO inhibitors have been discovered, and FTO inhibitors suppress cell growth in various types of cancer. FTO inhibitors were firstly identified by structure based virtual screening and biochemical analyses. Among these inhibitors, the natural compound Rhein competitively binds to the FTO catalytic domain and exhibits effective inhibitory activity on m^{6}A demethylation both *in vivo* and *in vitro*.[93] Meanwhile, Yang et al reported that Rhein significantly reduces the viability, induces apoptosis and cell cycle arrest in NSCLC cells,[94] however, the inhibitory

effect of Rhein on FTO in NSCLC still needs further investigation. Meclofenamic acid (MA) can selectively inhibit FTO by competing binding to the surface of FTO active site, and increases the level of m^{6}A modification in cells.[95] As an ethyl ester derivative of MA, MA2 suppresses glioblastoma stem cell growth and self-renewal *in vitro* and reduces tumor growth *in vivo*.[96] 4-chloro-6-(6′-chloro-7′-hydroxy-2′,4′,4′-trimethyl-chroman-2′-yl) benzene-1,3-diol (CHTB) and N-(5-Chloro-2,4-dihydroxyphenyl)-1- phenyl-cyclobutanecarboxamide (N-CDPCB) have been identified as FTO inhibitors by virtual screening. Structural studies proved that CHTB binds to the surface of FTO active site, while N-CDPCB is sandwiched in FTO.[97,98] A metabolite of mutant IDH1/2 enzymes, R-2-hydroxyglutarate (R-2HG), inhibits FTO activity and elevates m^{6}A level by binding to FTO directly. It enhances the YTHDF2 mediated degradation of MYC and CEBPA, and causes cell growth inhibition, cell-cycle arrest and apoptosis of acute myelocytic leukemia (AML).[99] In addition, R-2HG also exerts synergistic effects with other chemotherapy drugs against leukemia and glioma. Huang et al reported that another inhibitor of FTO, FB23-2 suppresses the proliferation and promotes differentiation of AML cells.[100] Both FTO and ALKBH5 are α-ketoglutarate (α-KG) dependent dioxygenases. They are highly expressed in isocitrate dehydrogenases (IDH) mutant cancers and could be inhibited by D2-hydorxyglutarate (D2-HG) by competitive binding.[101,102]

Besides FTO inhibitors, Weng et al reported that hematopoietic transcription factor SPI1 inhibits METTL14 expression and malignant hematopoiesis by regulating the METTL14-MYB/MYC signaling axis.[103] Zhang et al showed that a member of the carbonic anhydrases, carbonic anhydrase IV inhibits the tumorigenicity of colon cancer by inducing WTAP degradation and promoting the transcriptional activity of the Wilms' tumor 1 (WT1), which is an antagonist of WNT pathway.[104] S-adenosylmethionine is a cofactor substrate in METTL3-METTL14 complex. By competing with adenosylmethionine, a derivate of S-adenosylmethionine, S-adenosylhomocysteine inhibits the activity of some methyltransferases.[105]

The development of inhibitors of m^{6}A methylation regulators is still in its early stages. The improvement on specificity and efficacy of inhibitors are key issues, and this depends on further understanding of the mechanism of m^{6}A modification.

Conclusions and future perspectives

Numerous studies have revealed that m^{6}A RNA methylation controls RNA life including RNA transcription, splicing, processing, translation and decay. It also plays important roles in a broad range of biological processes such as cell proliferation, differentiation and embryonic development. In particular, m^{6}A RNA methylation is often dysregulated in tumors, and plays crucial roles in tumorigenesis and tumor progression through regulating oncogenes and tumor suppressor genes.

Although great progress has been achieved, there are still many fields warrant further investigation: (a) the discovery of novel 'writers', 'erasers' and 'readers'; (b) the study on the mechanism of RNA modification; (c) the development of quantitative technologies to detect RNA modification precisely; (d) the establishment of the profile of modified RNAs for cancer diagnosis and prognosis; (e) the development of novel anti-cancer drugs via targeting RNA modification. We hope the exploration of the mechanism of m^{6}A modification and the development of inhibitor of m^{6}A regulators will pave a new path for cancer therapy.

Author contributions

Qicheng Zhang selected literature, drafted the manuscript, and prepared the figure and table. Ke Xu designed this review, discussed and revised the manuscript. All authors contributed to this manuscript. All authors read and approved the final manuscript.

Conflict of interests

Authors declare no conflict of interests.

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