Proceedings of the 3rd International Conference on Environmental Geoscience and Earth Ecology
DOI: 10.54254/2753-8818/2025.22554

The Impact of N6-methyladenosine on RNA in Lung Cancer

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Abstract: Lung cancer can lead to the death of many people around the world and it is a challenge faced globally. The most common type of lung cancer is non-small cell lung cancer, and it accounts for 80% to 85%. In comparison, the proportion of patients with small cell lung cancer is relatively small, which is approximately 10% to 15%. In gene editing, m6A (N6-methyladenosine) refers to the methylation of adenosine on RNA at the 6th nitrogen atom. It is a common type of RNA modification that affects processes such as RNA stability, splicing, translation, and degradation. Regulating the m6A modification level of specific genes can play an important role in certain aspects of lung cancer RNA. m6A regulatory factors including 'writers', 'erasers' and 'readers' play crucial roles in various biological processes related to RNA metabolism and gene expression. Their functions can exert an influence on the treatment of lung cancer. This view will discuss the functions of m6A methylation modification on the stability, translation and non-coding part of RNA and the newest treatment methods act m6 modification as the therapeutic target for lung cancer.

Keywords: m6-methyladenosine, lung cancer, RNA

1. Introduction

The main reason for global cancer death is lung cancer [1]. The most common ordinary types of lung cancer are divided into two sorts including small-cell lung cancer and non-small-cell carcinoma of the lung (NSCLC) which contains adenocarcinoma (cancer of the glandular), squamous cell carcinoma (SCC), and large-cell Carcinoma (LCC). Meanwhile, cases of non-small-cell carcinoma occupy 80%-85% of all cases in lung cancer, and SCLC cases account for 10%-15% [2]. The malignant proliferation of lung epithelial causes lung cancer [3]. The malignant proliferation is related to abnormal expression and malfunction of regulation in RNA. The m6A site is enriched near the stop codon and 3'-untranslated region (UTR), and m6 residues have a relative connection with the mRNA binding sites in the 3'-UTR [4]. N6-methyladenosine (m6A) indicates that the methylation of the sixth nitrogen position in RNA molecules is a common modification that influences RNA stability, splicing, and degradation. The m6 methyltransferase, demethylases, and protein that can identify and combine m6 modification sites play a significant role in this process. The m6 methyltransferase is a kind of enzyme that catalyzes m6-methyladenosine in lung cancer tissue composed of METTL3, METTL14, METTL16, and WTAP [5]. METTL3 acts as a 'writer' that is an adenosyl methionine-binding protein which is responsible for m6 modification [5]. It catalyzes the methyl groups of S-adenosyl methionine (SAM) which transfers to adenine bases in RNA, generating S-adenosyl homocysteine (SAH). The total level of N6-methyladenosine can be

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DOI: 10.54254/2753-8818/2025.22554

affected by abnormal expression of METTL [4]. Meanwhile, the METTL3-METTL14 heterodimer core complex is a stable compound comprised of METTL3 and METTL14. Also, the METTL3-METTL14 complex and WTAP have an effect on the deposition of cellular m6A [5].

The demethylases are referred to as 'erasers' and have the ability of removing the m6A modification. From now on, only obesity-associated protein (FTO) and the AlkB homolog 5 (ALBHB) are identified and belong to alpha-ketoglutarate-dependent dioxygenase. Also, the main position of these proteins is the m6A demethylated cell nucleus. Through marking the m6-rich region in RNA, FTO utilizes the oxidative activity for mediating demethylation [6]. The function of FTO improves the dynamic reversible process of m6A modification [7]. FTO retains the ability of demethylation and depends on single-guide RNA and PAMmer in a manner of sequence specificity combined with RNA [6]. FTO makes an interaction with RNA and the catalytic activity relies on the interplay with catalytic residues and nucleobase which is determined by RNA sequence and tertiary structure [6]. Besides, ALKBK5 has the same ability as FTO which both are specific. ALKBH5 catalyzes m6A demethylation in RNA and attends to splice and form longer 3'UTR mRNA [6]. The reader is composed of m6A regulatory factors which include YTH domain family proteins (YTHDF1-3) and YTH domain-containing proteins (YTHDC1-2). The YTHDC1-2 has a conservative m6A combined domain [8]. YTHDF2 integrates mRNA which is decorated by m6A selectively and regulates RNA degradation. Compared with YTHDF2, YTHDF1 is major to control mRNA transport. YTHDF1 bonds with m6A site of mRNA that is near to stop codon, and raises to translate initiation complex (including elF3, elF4E, and poly(A) combined protein). Also, it can promote the translation of target RNA with 40S ribosomal subunit [9].

2. The Influence of N6-methyladenosine on RNA Stability

N6-methyladenosine can regulate RNA degradation to influence the stability of RNA. Liu et al. indicated that METTL3, METTL14, and WTAP silencing bring about abundance of m6-targeted transcript increases remarkably by comparing the spreading of the transcriptome-wide in the same cell line with PAR-CLIP sites. The reduction of total m6A methylation level might be the extent of nascent RNA lifetime [5]. Meanwhile, the 'writers', 'easers', and 'readers' control N6-methyladenosine in affecting RNA metabolism and protein expression that negative regulates in a posttranscriptional manner [10]. It suggests that the modification of N6-methyladenosine can change the mRNA secondary structure which can affect the interaction between the binding protein with RNA and the binding factor. Then, it has an impact on RNA stability.

The oncogene and tumor suppressor gene of mRNA can raise the specific RNA binding protein to promote mRNA degradation after N6-methyladenosine in lung cancer. METTL3 knockdowns the growth substantially of cadherins' expression and decreases the levels of fibronectin and vimentin. This is also able to inhibit the expression change of simulating epithelia-mesenchymal transition's relatively notation handling by transforming growth factor. As a result, metastasis-associated lung adenocarcinoma transcript 1 increases [7]. Moreover, METTL3 prevents the occurrence of LTHDC2 via regulating SLC7A11 mRNA [11]. From this process, the knockdown of METTL3 dramatically expedites solute carrier family 7 member 11 (SLC7A11) decayed half-life, indicating the opposite effect because of overexpression [12]. Therefore, this process may have an influence on the rate of degradation. However, the overexpression of Yes-associated protein (YAP) medicated by METTLE can lead to tumor metastasis. It can upregulate the metastatic ability of m6A level that enhances the translation of YAP and activates the MALAT1-miR-19143p-YAP axis to increase the stability of YAP metastatic ability [11].

Concurrently, FTO acts as 'erasers' which also have responsible for impacting the influence on RNA stability in controlling the relative protein in tumors. With the high level of FTO, the degree of N6-methyladenosine in LC can be dropped. While knocking out FTO, CLIC5's N6-

methyladenosine may be increased. In addition, the researcher discovered that FTO can combine with one of the sequences among the sequences related to m6A modification in Chloride intracellular channel protein 5 (CLIC5) [13]. It shows that the binding of FTO to the RNA sequence related might influent RNA structure and function, then affecting RNA stability. Moreover, ALKBH5 is another kind of demethylase to affect mRNA stability. Tissue Inhibitor of Metalloproteinases' mRNA is inhibited by ALKBH5 which enhances the proliferation capacity of NSCLC cells and reduce apoptosis [6]. The 'reader', YTHDF1, plays an important role in the occurrence and removal of Lung Adenocarcinoma. FTH serves as a kind of related protein in iron metabolism which is dropped by YTHDF1 to inhibit the proliferation and metastasis of lung cancer cells [13]. YTHDF2 binds to the N6-methyladenosine mRNA selectively and regulates the degradation of RNA. C-terminal area of YHDF2 recognizes the specific site. The N-terminal area associated with the SH structural domain in the CCR4-NOT transfer complex1. Thus, this process can recruit the CCR4-NOT splicing complex and transport RNA to the processing body (P-body) to speed up the degradation [4].

3. The Influence of N6-methyladenosine on RNA Translation

N6-methyladenosine can have an interaction with the initiation factor and ribosome and play a role in the translate stage. Then, it is able to enhance the initiation efficiency. In lung ribosomes, the mRNAs of some oncogenes modified by N6-methyladenosine can raise ribosomes effectively and increase the amount of expression, promoting the growth of oncogenes. METTL3 interplay with translation initiation factor, causing specifically improved initiation factor-dependent reporter mRNAs translation [6]. METTL3 regulates gene translation through many mechanisms which can activate the translation of epidermal growth factor receptors and tafazzin to promote the growth, survival, and invasion of lung cancer cells [4]. METTL3 raises the eukaryotic translation initiation factor (elF3) to the translated compound of H1299 cells. The interplay of METTL3-elF3H is important for promoting the translation and forming dense ribosomes [7]. METTL3 also can increase the translation of RNA via directly recruiting translation initiation factors. METTL3 knocks out the inhibit recruitment including elF3 to cap-binding protein 80 and elF4E-cap binding proteins [7]. Meanwhile, the mRNA of METTL3 can modify CTNNB1 which is the genetic code of the β-catenin protein in the 5'UTR area and, negatively modulation the translation of CTNNB1 mRNA. So, METTL3 upregulates the expression of E2F2 regulatory factors and downregulates β-catenin protein [11].

The domain family members of The YT521-B homology which includes YTH domain family proteins and YTH domain-containing proteins have a conserved binding domain [4]. YTHDF1 can promote the synthesis of protein via translated mechanisms' interaction [7]. Therefore, METTL3 and YTHDF1 can enhance the translation through interaction. YTHDF1 recognized METTL3-mediated m6A-methylated SLC7A11 mRNA and can be recruited to regulate the stability and translation of SLC7A11 by METTL3 [12]. Also, YTHDC2 increases the occurrence rate of targeting mRNA translation via declining its redundancy [10]. In the cytoplasm, m6A-binding protein YTHDF1 and, promotes mRNA translation in N6-methyladenosine and YHDF2 can facilitate the decay of transcripts which is modified by N6-methyladenosine [7]. YTHDF2 binds to the m6A site near the stop codon and recruits' translation initiation complex which includes elF3, elF4, poly(A) binding protein (PABP) and, 40S ribosomal subunit to promote target RNA translation. YTHD3 collaborates with YTHDF1 and initiation factor elF4A3 which encourages RNA translation and mRNA decomposition [4]. Meanwhile, YTHDF and YAP family have double functions which YTHDF1/3 can facilitate YAP mRNA translation through the interaction with elF3a/elF3b. The lack of YTHDF1 may have an influence on the translation efficiency of cyclin. As a result, this process can inhibit proliferation and the form of colony and xenograft tumors [7].

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4. The Influence of N6-methyladenosine on Non-coding RNA

The non-coding which acts as functional RNA cannot be translated to protein but can regulate the expression of genes. With regards to length, they can be divided into short-chain noncoding RNA (including siRNA, miRNA, and piRNA) and long-chain noncoding RNA (lncRNA) [11]. M6A can have an impact on the biosynthesis process of miRNA including pri-miRNA manufacture and pre-miRNA maturity. At the same time, N6-methyladenosine appears to change the expression level of miRNA. This can affect the regulatory function of the target gene. In contrast, it can inhibit some cancer-promoting miRNA manufacture, diminish and other cancer-promoting functions. miRNA is able to regulate the expression of target genes after transcription through incomplete complementary pairing with mRNA 3'UTR. 67% of transcription factors in 3'UTR contain at least one miRNA binding site. Thus, METTL3-mediated m6A methylation modification is highly correlated with miRNA [11]. Through a series of mediated by m6A regulatory proteins, m6A has an effect on miRNAs including let-7e, miR-25, miR-93, miR-126, miR221/222, and miR-4485. These are stability levels of miRNAs which may be subject to the change of METTL3 and enhance the biosynthesis of miRNA [13]. miRNA can express differences and play a role in oncogenes and tumor suppressor genes which is based on miRNA's regular function. According to the report, METTL3 can increase precursor miR-143-3p splicing and accelerate the process and mature of miR-143-3p [7]. At the same time, METTL3-YHDC1 attends the process of circRNA reverse shearing. For example, the knockdown of circPUM1 inhibits glycolysis and the NSCLC cells' growth in in vivo and vitro [11]. A new RNA methyltransferase NSun2 interrupts the drop of miR-125B and is confirmed to disturb A549 cells which mature processing miR-125b from pri-miR-125b2 and pre-125b2 [7].

Also, N6-methyladenosine can affect the lncRNA function. It may change the secondary structure of lncRNA and other molecular mutual interactions, causing lncRNA regulatory function in lung cancer. lncRNA MALAT1 and miR-1914-3p can be regulated by YAP mRNA which stability increase can enhance the drug resistance of NSCLC and metastasis by METTL3 [6]. The report indicated that m6A-long non-coding RNA epitranscriptomic microarray can identify the HNRNPA2B1 molecular mechanism. According to the result of the experiment, the N6-methyladenosine lncRNA level changes through knocking out HNRNPA2B1. Also, the change of HNRNPA2B1 has an influence on lncRNA expression [14]. Both of them can indicate that N6-methyladenosine has an impact on lncRNA function. As for the structure, some N6-methyladenosine lncRNA can form RNA-RNA double-strand composition and affect mRNA stability and translation or combine with protein and regulate the site and activate protein.

5. N6-methyladenosine Modification as the Therapeutic Target for Lung Cancer

N6-methyladenosine plays a crucial part in the gene regulation of lung cancer cells. m6A regulatory factors are a good way to therapeutic and intervention lung cancer due to its safety. Although m6A regulatory factors show an up-regulation in expression in lung cancer, the expression is limited in non-malignant tissues and cells of the patient [13]. METTL3 has a relationship with apoptosis, affecting the proliferation and drug resistance of lung cancer cells. The promotion of lung cancer cells proliferation is caused by METTL3 increasing the stability of lncRNA ABHD11-AS1and HNRNPA2B1 regulates the expression of lncRNA MEG3 which is a kind of tumor suppressor factor and the expression level is down-regulated in non-small cell lung cancer (NSCLC) via N6-methyladenosine [7, 14]. Meanwhile, FTO can reduce the expression of CLICS which overexpression can inhibit lung cancer cells' proliferation through collaborating with demethylate the M6 modification site of CLICS [13]. And, YTHDF2 promotes lung cancer cells' growth through accelerating the translation of 6PGD mRNA [13]. On the other hand, the research indicated

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that the m6A enrichment score of H1299 is higher than in A549 while analyzing the relationship between N6-methyladenosine and the drug resistance of H1299 in non-small cell lung cancer cells. This means that N6-methyladenosine leads to non-small cell lung cancer developing resistance to H1299, as interfering with the normal cell cycle [3]. Also, FTO and ALKBH5 effect immunotherapy response in lung cancer cells by reducing N6-methyladenosine, leading to PD-1 drug resistance [10]. These are the reasons why N6-methyladenosine can be a therapeutic target for lung cancer.

Researchers indicated that YTHDC2 can serve as an endogenous ferroptosis inducer for LUAD patients. A new inflammatory programmed cell death pathway called ferroptosis features iron accumulation and lipid peroxidation induced through constraining the xCT/GSH/GPX4 axis. And, YTHDC2 can regulate the site of m6A in 3'UTR to suppress SLC3A2 expression [10]. The other therapeutic approach is Cisplatin which is a kind of metallic complex the possessed anticancer activity. The drug resistance of Cisplatin can be changed by m6A regulatory factors modification. For example, the upregulation of METTL3 increases the expression of AKT1 and the lack of YTHDF1 effects on Keap1/Nrf2 [4]. At the same time, FTO inhibitors can play a role in suppressing different kinds of cancer cells' growth. In these inhibitors, the competitive binding between the natural compound Rhein and the FTO catalytic domain exhibits effective inhibitory activity to m6A demethylation in vivo and in vitro [6]. This is able to restore the function of the tumor suppressor gene and achieve the goal of treating lung cancer.

6. Conclusion

N6-methyladenosine is a new technology on the influence and treatment including the processes of RNA stability, splicing, translation, and degradation. The m6A regulatory factors contain 'writers' (METTL3, METTL4, METTL16, and WTAP), 'erases' (FTO and ALKBK5) and 'readers' (m6A regulatory factors) which make a substantial contribution to RNA stability, translation, and non-coding genes to regulate the expression of oncogenes and tumor suppressor genes in lung cancer. For the RNA stability, the m6A regulatory factors modulate mRNA degradation by recruiting specific RNA-binding proteins. For instance, METTL3 facilitates the N6-methyladenosine of key oncogenes genes mRNA to decrease the stability of the mRNA, then it affects the metastasis and proliferation of lung cancer cells. On the other hand, N6-methyladenosine exerts an influence on RNA translation by enhancing translation initiation through efficiently recruiting ribosomes to increase the expression of related cancer-associated proteins. For example, some translation initiation factors can enhance their binding affinity to the m6A modifications in the 5'UTR regions of proto-oncogene mRNAs. As a result, the translation efficiency is improved, leading to the abundant expression of relevant oncoproteins in cancer cells. The impact on non-coding RNAs is also an issue related to m6A modification in regulating miRNA processes and functions. The biogenesis process of miRNA and lncRNA will be altered by m6A methylation modification, thus leading to changes in the regulation of target genes. m6A can promote the maturation of tumor-suppressor miRNAs and inhibit the processing of certain miRNAs, thereby suppressing the proliferation of lung cancer cells and attenuating the cancer-promoting functions, respectively. At present, it is regarded M6 Modification as a very promising target for the treatment of lung cancer because of its safety, drug resistance profile, and its effect on the expansion of cancer cells. Currently, some treatment regimens targeting m6A methylation modification have been developed such as some kinds of FTO inhibitors and using YTHDC2 sever as an endogenous ferroptosis inducer. Although the treatment of m6 methylation modification has achieved excellent results, it is still necessary to conduct further research on how m6A modification affects the cellular components (such as immune cells, fibroblasts, etc.) and the cytokine network in the tumor

DOI: 10.54254/2753-8818/2025.22554

microenvironment. At the same time, it can focus on the treatment with m6A modification, when combined with immunotherapy and chemotherapy, enhancing the immunogenicity of antigens.

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