Review Article

Association between methyltransferase-like 3 and non-small cell lung cancer: pathogenesis, therapeutic resistance, and clinical applications

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Abstract: Non-small cell lung cancer (NSCLC) is a malignant cancer that with high incidence, recurrence, and mortality rates in human beings, posing significant threats to human health. Moreover, effective early diagnosis of NSCLC remains limited primarily by the lack of accurate biomarkers. Therefore, there is an urgent need to understand the mechanisms underlying NSCLC pathogenesis and treatment failure. Methyltransferase-like 3 (METTL3) is a prototypical member of a family of which its members transfer methyl groups. It has been implicated in modulating the pathogenesis of NSCLC, as well as conferring resistance to NSCLC therapeutics. The targeting of METTL3 for NSCLC treatment has been reported. However, the relationship between METTL3 and NSCLC remains to be demonstrated. In this review, we discuss relevant interrelationships by summarising the studies on METTL3 in NSCLC pathogenesis, therapeutic resistance, and clinical applications. Current research suggests that the upregulation of METTL3 expression propels the tumorigenesis, progression, and treatment resistance of NSCLC. Therefore, we propose that METTL3 is an excellent candidate biomarker for NSCLC diagnosis and prognosis. Therapeutic targeting of METTL3 has significant potential for NSCLC treatment. This review provides a summary of the association between METTL3 and NSCLC, which would be a valuable reference for both basic and clinical research.

Keywords: Methyltransferase-like 3 (METTL3); non-small cell lung cancer (NSCLC); pathogenesis; therapeutic resistance

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Introduction

Non-small cell lung cancer (NSCLC) is a common malignancy worldwide (1). Currently, effective early diagnosis of NSCLC remains limited primarily by the lack of accurate biomarkers, and NSCLC is usually diagnosed late in its progression (2,3). Clinical strategies for NSCLC treatment usually have a high risk of recurrence and metastasis, with

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5-year survival of less than 30% after treatment (4,5). Given these characteristics, there is an urgent need to understand the mechanisms underlying NSCLC pathogenesis and treatment failure.

Both pathogenesis and therapeutic failure are often accompanied by intricate mechanisms, encompassing genetic factors and environmental influences (5,6). Currently, the rapid advancement of sequencing technologies, including RNA-seq and MeRIP-seq, has improved our understanding of epigenetic modifications at the post-transcriptional level (7-9). In particular, the most quintessential post-transcriptional regulation of gene function, RNA N^6-methyladenosine (m^6A), in NSCLC has been extensively documented (10). This effect on RNA, specifically RRACH (R for A or G, H for A, U or C) is dynamically governed by three key enzymes that are often called "writers, erasers, and readers" (11,12). Writers primarily include the methyltransferase complex of methyltransferase-like 3/14 (METTL3/14)-WT1-associated protein (WTAP), which adds methyl groups ($-CH_3$) to the sixth nitrogen atom of adenines of newly transcribed RNAs (naïve RNAs). Erasers include demethylases, including fat mass and obesity-associated protein (FTO), and AlkB homolog 5 (ALKBH5) that remove methyl groups (11,13). These modifications by writers and erasers transmute naïve RNAs into pre-RNAs, which subsequently undergo further splicing modifications to produce mature RNAs, which are then transported out of the nucleus. Readers, including YTH N^6-methyladenosine RNA binding protein (YTHDF), YTHDF domain-containing protein (YTHDC), heterogeneous nuclear ribonucleoparticles (hnRNPs), and insulin-like growth factor 2 mRNA-binding protein (IGF2BP), discern these mature RNAs, influencing both their stability and translation (11-13) (*Figure 1*).

The METTL protein family is composed of METTL3, 4, 5, 14, 16, and 25B, which share a conserved S-adenosyl methionine binding domain and contribute to m^6A modification (14). Specifically, METTL3, together with METTL14 and WTAP, forms the primary heterocomplex of m^6A writers (14). Other METTL family members form the auxiliary structures involved in catalysis. METTL3 is the primary m^6A-producing enzyme and the only subunit with catalytic activity, whereas METTL14 lacks catalytic activity and is commonly considered a structural subunit that binds to target RNA, promoting the action of METTL3 (15). METTL3 is predominantly localized to human chromosome 14q11.2, with pronounced enrichment in nuclear speckles. METTL3 is also present in the cytoplasm, possibly engaging in methyltransferase-independent functions related to translation initiation (16,17). As studies on METTL3-mediated RNA m^6A modification have progressed, studies have highlighted the active involvement of METTL3 in both NSCLC pathogenesis and therapeutic resistance, as well as using METTL3 as a potential therapeutic target (17-19). However, a comprehensive analysis of these studies to discuss the relationship between METTL3 and NSCLC, as well as suggestions for the prospective applications of METTL3 in clinical settings, is currently lacking.

To address this gap in literature, we reviewed the current understanding of the roles and mechanisms of METTL3 in NSCLC. Furthermore, we suggest prospective applications and future perspectives of METTL3 (*Figure 2*).

METTL3 contributes to NSCLC tumorigenesis and progression

Recent epigenetic study has revealed a strong correlation between RNA m^6A modification by METTL3 and both tumorigenesis and malignant progression of NSCLC (18). This modification plays a significant role in the general regulation of cancer-cell proliferation, migration, and invasion (20). Moreover, METTL3-mediated m^6A modification regulates the epithelial-mesenchymal transition (EMT), abnormal angiogenesis, and the tumour microenvironment (TME) by targeting multiple RNAs (18). METTL3 is a potential independent prognostic factor to predict NSCLC survival (21).

METTL3 functions in NSCLC by regulating mRNAs

Mutations in multiple critical genes, including those encoding epidermal growth factor receptor (*EGFR*), *TP53*, and *KRAS*, contribute to the onset and progression of NSCLC (22). Interestingly, *METTL3* expression is increased in patients with NSCLC with *EGFR* exon 19 mutations compared with patients with wild-type *EGFR*; this promotes EMT, migration, and proliferation by regulating the translation of *EGFR* mRNA (23). Patients with NSCLC with high *METTL3* expression combined with *EGFR* mutations exhibit shorter progression-free survival compared to those with *EGFR* mutations and *METTL3* low expression, suggesting that *METTL3* and *EGFR* work synergistically (24). In contrast, the expression of METTL3 is downregulated in *KRAS* mutant NSCLC

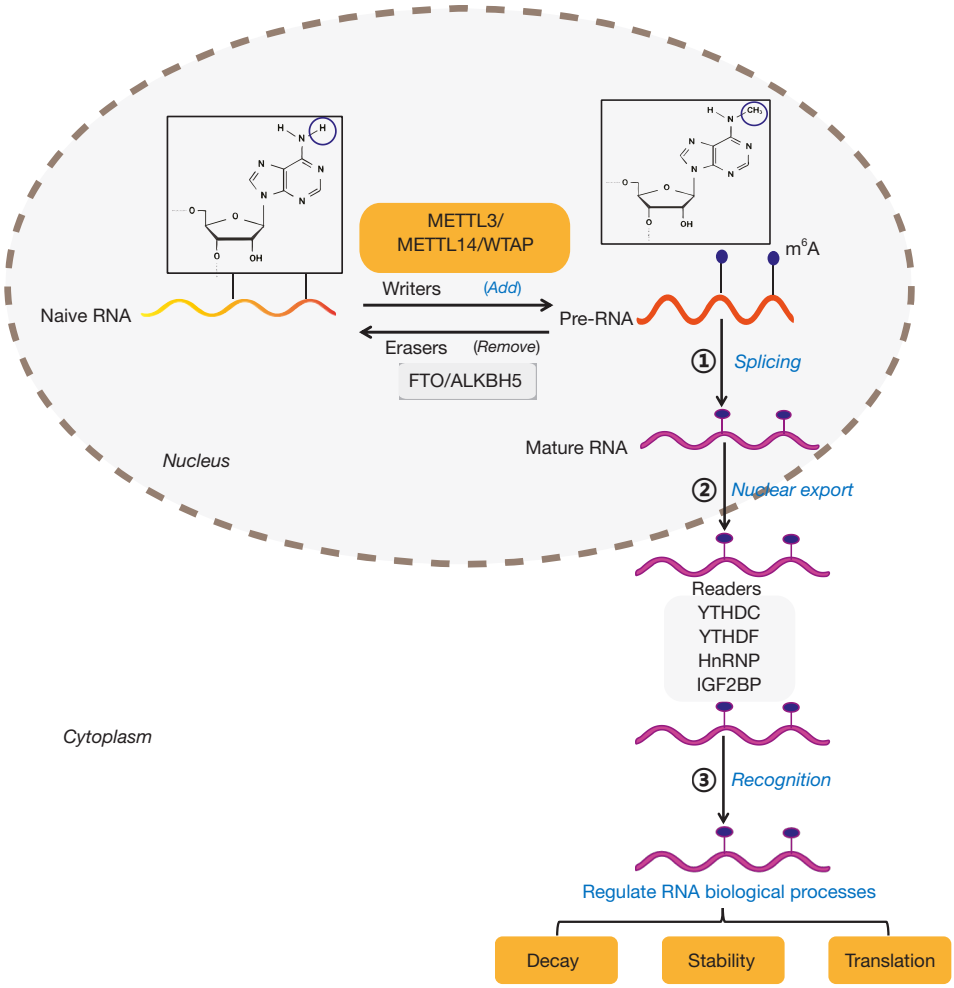

Figure 1 Mechanism underlying the m6A modification of RNAs. RNA m^{6}A modification is mediated by a complex interplay among writers (METTL3, METTL14, and WTAP), erasers (FTO and ALKBH5), and readers (YTHDC, YTHDF, HnRNP, and IGF2BP). This process involves the addition and removal of-CH_3 from naive RNA to form a pre-RNA, which is then spliced into mature RNA. These modifications ultimately regulate RNA decay, stability, and translation. Specifically, METTL3 recognizes and catalyses the RRACH (GACU) sequence motif by transferring a methyl group onto its adenosine residue.

tissues (24). Compared with the expression levels in *TP53* non-mutated NSCLC tissues, *METTL3* expression is not significantly altered in *TP53*-mutant NSCLC tissues (25).

Cigarette smoking is a major risk factor contributing to both onset and progression of NSCLC by upregulating METTL3 expression, which subsequently silences tumour-suppressor gene expression or activates oncogenes expression that are regulated by METTL3-mediated RNA m^{6}A modification (26,27). For example, hypoxia-inducible factor-1 alpha (HIF-1α) is a key transcription factor in cancer (28). High expression of HIF-1α and downstream genes promotes cancer progression through multiple mechanisms (28). Cigarette smoking increases HIF-1α expression that, in turn, increases METTL3 transcription in NSCLC (29). Increased METTL3 expression mediates m^{6}A modification of cyclin-dependent kinase 2-associated protein 2 (*CDK2AP2*) mRNA, suppressing CDK2AP2 expression that promotes cell-cycle and NSCLC progression (29). Death-associated protein kinase 2 (*DAPK2*), a tumour suppressor gene, contributes significantly to smoking-related NSCLC progression. Jin *et al.* (30) demonstrated that METTL3 and YTHDF2

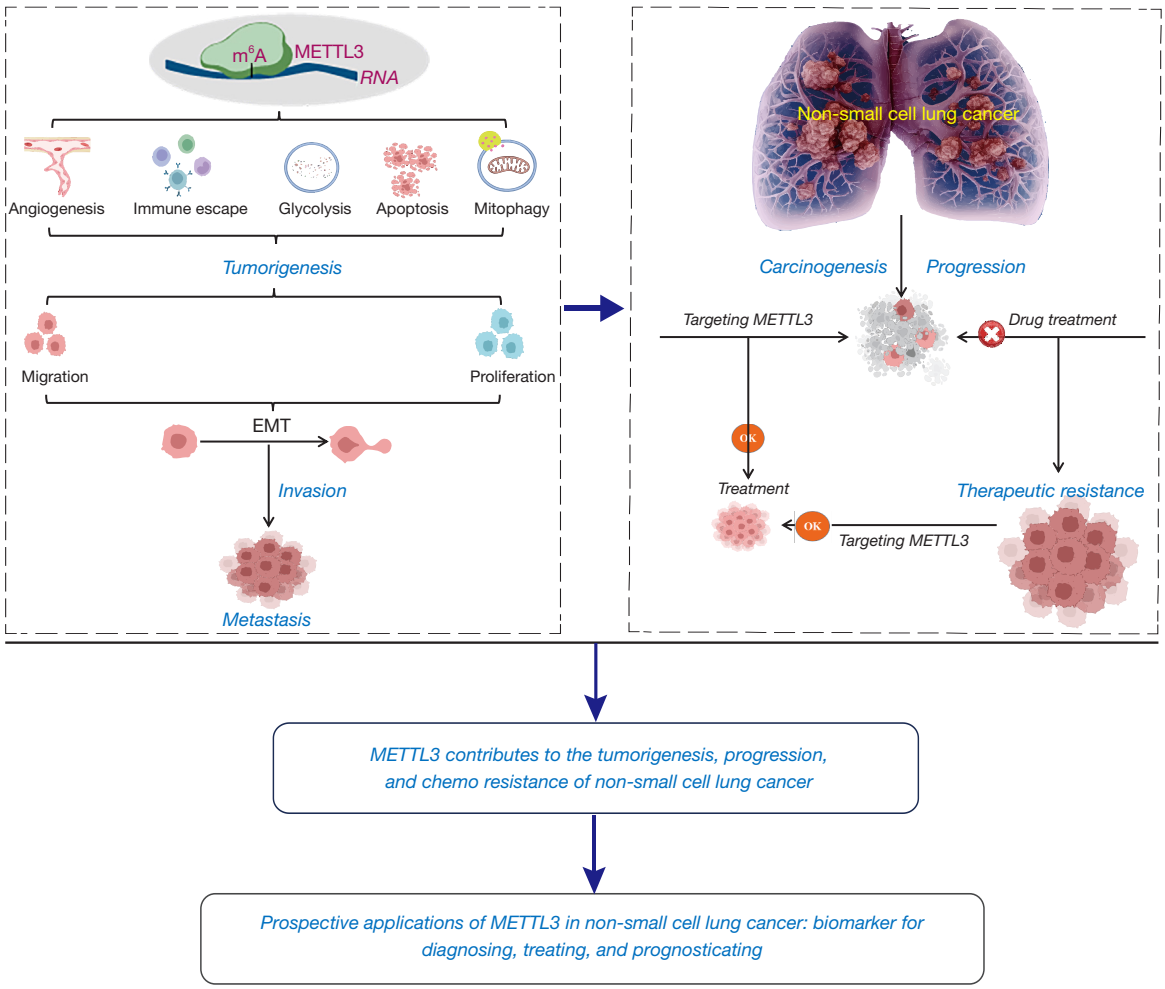

Figure 2 METTL3-mediated RNA m^{6}A modification in NSCLC. Mechanisms of METTL3 in the carcinogenesis and therapeutic resistance of NSCLC are analysed, providing an interrelationship interpretation of the pathogenesis of NSCLC from the novel perspective of METTL3-mediated RNA m^{6}A modification. Clinical applications of METTL3 in NSCLC as a biomarker for diagnosis, treatment, and prognosis are suggested. NSCLC, non-small cell lung cancer; EMT, epithelial-mesenchymal transition.

induce aberrant m^{6}A modification of *DAPK2* mRNA in NSCLC tissues, resulting in the reduced expression of DAPK2, which significantly facilitates the proliferation and migration abilities of NSCLC by activating the nuclear factor (NF)-κB signalling pathway. Secreted frizzled-related protein 2 (*SFRP2*) also inhibits NSCLC. Zhao *et al.* (31) found that METTL3 negatively regulates SFRP2 expression, which, in turn, activates the Wnt/β-catenin signalling pathway to promote NSCLC tumorigenesis. Consistent with this study, the Fraser syndrome protein 1 (*FRAS1*) transcript undergoes METTL3-regulated m^{6}A modification that correlates with poor prognosis in NSCLC (32). The METTL3-FRAS1 axis contributes to NSCLC cell proliferation, colony formation, and tumour growth by regulating *CDON* which cooperates with YTHDF1 (32). Furthermore, *METTL3* acts as an oncogene directly by promoting *BCL2* mRNA translation and expression via m^{6}A modification in NSCLC, enhancing the viability and migration of tumour cells (33).

Lung adenocarcinoma (LUAD), the dominant type of NSCLC, is common in non-smokers and typically arises from the smaller bronchial epithelium (34). LUAD tissue often has poorly defined boundaries; moreover, it is frequently accompanied by fibrosis and subleukocyte scar formation (35). Current LUAD analyses have revealed significant increases of METTL3 expression in cancer

tissues, demonstrating its pivotal role in the pathogenesis of LUAD, as well as strong links to decreased overall survival (36,37). A large amount of evidence has demonstrated the significant roles of METTL3 in LUAD, including stemness maintenance, proliferation promotion, migration facilitation, progression acceleration, and apoptosis inhibition (36,37). The function of METTL3 in LUAD onset is contingent on its methyltransferase activity. For example, enolase 1 (ENO1) is a glycolysis enzyme, which participates in cancer progression. Ma *et al.* (38) reported that the increased METTL3 expression facilitates the binding of *ENO1* mRNA with YTHDF1, resulting in enhanced ENO1 translation. This consequently promoted spheroid generation in LUAD cells and intrapulmonary tumour formation in mice by stimulating glycolysis and tumorigenesis in patients with LUAD. Similarly, Choe *et al.* (39) reported that increased METTL3 expression enhances the translation of oncogenic bromodomain-containing protein 4 (*BRD4*) mRNA, thereby promoting LUAD tumorigenicity. F-box and WD repeat domain containing 7 (FBXW7) functions as a tumour suppressor in human cancer. Wu *et al.* (40) reported that METTL3 functions in increasing m^{6}A modification of *FBXW7* mRNA, promoting its translation, inhibiting apoptosis while promoting proliferation in LUAD cells (40).

EMT is a significant factor in tumour progression (41). Current study has suggested significant contributions of METTL3 to its regulation by targeting multiple mRNAs. For example, JUNB is a dominant transcriptional regulator of EMT (42). A study by Wanna-Udom *et al.* (42) demonstrated that the increased expression of METTL3 in LUAD enriches m^{6}A modification of *JUNB* mRNA and promotes its stability, which subsequently leads to transforming growth factor β-induced EMT, facilitating LUAD progression. In line with this, it has been shown that in an inflammatory microenvironment, interleukin (IL)-6 transcriptionally activates *METTL3* expression (43). This activation promotes the proliferation, migration, invasion, and EMT of LUAD cells by increasing Yes-associated protein 1 (*YAP1*) mRNA expression, activating the YAP1/TEAD signalling pathway (43). Trophinin-associated protein (*TROAP*) mRNA expression is regulated by METTL3 and is highly expressed in NSCLC, which accelerates its progression through the PI3K/AKT and EMT pathways, suggesting TROAP as a novel target for NSCLC therapy (44).

Communication between tumour cells and the TME facilitates tumour growth by regulating immune escape, inflammation, and metastasis, contributing to the tumorigenesis and tumour progression (45,46). Cancer-associated fibroblasts (CAFs) are a major component of the TME that are linked strongly to NSCLC metastasis by mediating m^{6}A modifications in tumour cells (47-49). CAFs accelerate the malignant progression of tumours by producing cytokines and growth factors (49,50). For example, CAFs secrete collagen type X alpha 1 (COL10A1) and RAC3 that indicate poor prognosis in NSCLC. Li *et al.* (51) and Chen *et al.* (52) reported that the function of CAFs in NSCLC depends on METTL3 modification of *RAC3* and *COL10A1* mRNAs that upregulates their m^{6}A levels, stability, and translation. METTL3-modified *RAC3* and *COL10A1* promote NSCLC growth, suggesting that they are downstream targets of METTL3. The axes of METTL3-RAC3 and METTL3-COL10A1 may provide therapeutic targets for NSCLC treatment. Moreover, CAFs may secrete METTL3 (53). The CAF-derived METTL3 alleviates programmed cell death ligand-1 (PD-L1)-mediated immunosuppression of NSCLC by targeting *IL-18*. Subsequently, IL-18 enhances NSCLC immunosuppression by stimulating NF-κB signalling (53).

Together, these findings demonstrate that the abnormal expression of *METTL3* functions both directly as an oncogene and regulates oncogene expression indirectly. Specifically, the aberrant m^{6}A modification mediated by METTL3 on tumour-related genes such as *CDK2AP2*, *DAPK2*, *SFRP2*, *FRAS1*, *BRD4*, *JUNB*, *YAP1*, *TROAP*, *COL10A1*, and *RAC3*, as well as serving directly as an oncogene by regulating *Bcl-2*, *ENO1*, *FBXW7*, and *IL-18*, triggering the onset and exacerbating the progression of NSCLC, provides novel insights into the mechanisms driving NSCLC advancement, showing great potential for diagnosis and prognosis in NSCLC, and identifying a potential therapeutic target for patients with NSCLC (*Figure 3*).

METTL3 functions in NSCLC by regulating non-coding RNAs

Non-coding RNAs, including microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs) play important roles in NSCLC proliferation, apoptosis, migration, and invasion, in which METTL3 is essential for their regulation. For example, increased expression of METTL3 enhances miR-21-5p maturation, which, in turn, targets *FDX1* and increases tumorigenicity (54). Besides, Wang *et al.* (55) demonstrated that the increased expression

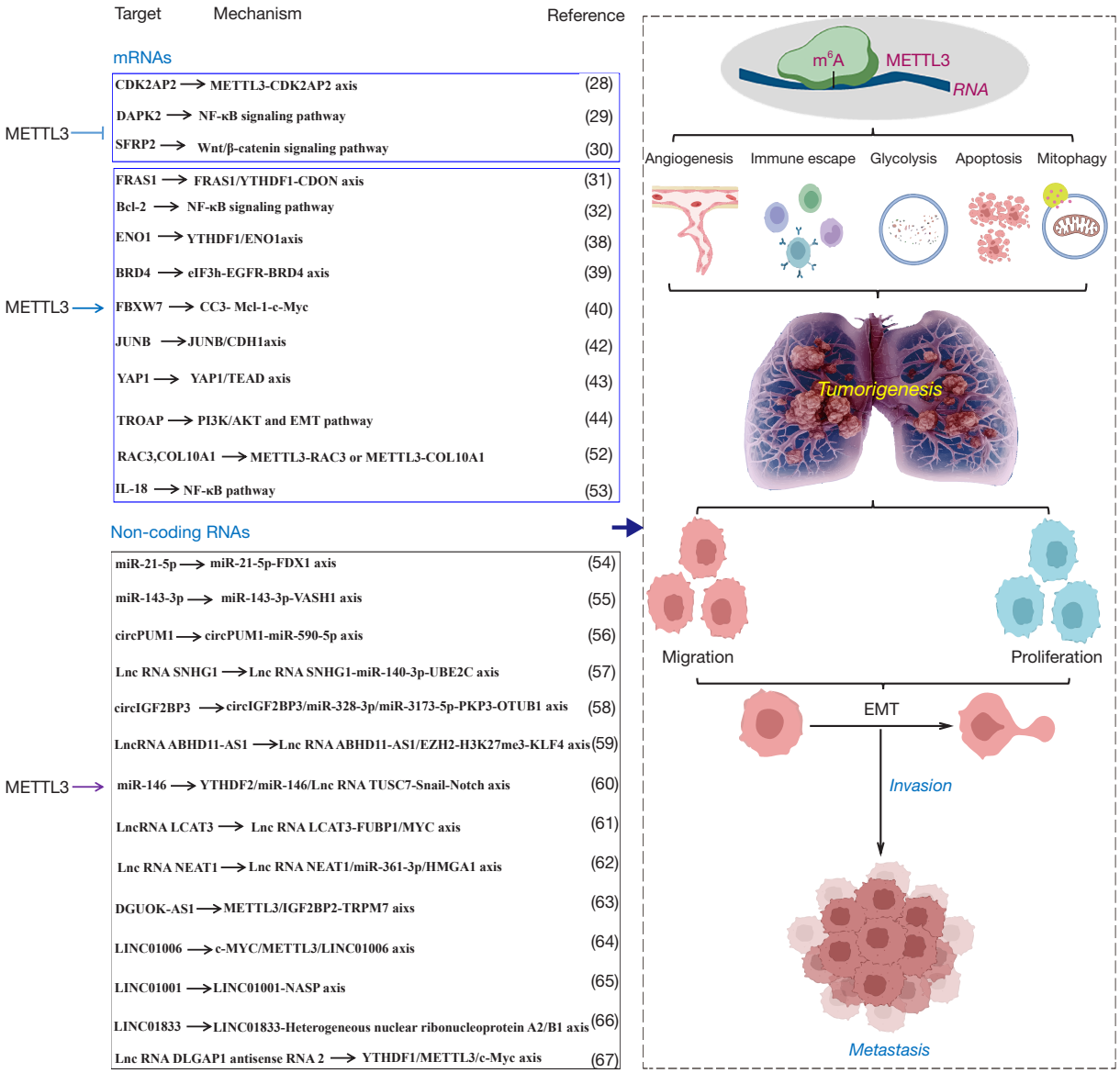

Figure 3 METTL3 contributes to the onset and progression of NSCLC. The targets, mechanisms, and roles of METTL3 [mRNAs (28-32,38-40,42-44,52,53), non-coding RNAs (54-67)] in NSCLC are summarised and analysed. Notably, METTL3 triggers and exacerbates these NSCLCs primarily by promoting angiogenesis, immune escape, EMT, and tumour cell biological functions (glycolysis, apoptosis, and mitophagy). NSCLC, non-small cell lung cancer; EMT, epithelial-mesenchymal transition.

of METTL3 promotes the splicing of a miR-143-3p precursor to enhance its biogenesis, augmenting lung cancer angiogenesis by targeting the 3'-untranslated region (3'-UTR) of vasotocin-1 (*VASH1*) mRNA and suppressing its expression. Therefore, METTL3/miR-143-3p/VASH1 axis is an unfavourable prognostic factor for the progression and overall survival rate of LUAD (55). Another study demonstrated that METTL3 is significantly upregulated in LUAD cell lines and regulates LUAD progression by interacting with miR-590-5p to increase the expression of its direct target lncRNA NUTM2A-AS1 (68).

RNA pumilio RNA binding family member 1 (circPUM1) plays important roles in the tumorigenesis of several cancers and is expressed in both NSCLC

tissues and cell lines (69). Li *et al.* (56) discovered that the increased circPUM1 expression leads to NSCLC tumour proliferation and glycolysis by downregulating miR-590-5p and upregulating METTL3. Ubiquitin-conjugating enzyme 2C (UBE2C), often overexpressed in cancers, plays an indispensable role in cancer progression (57). Given the correlation between UBE2C expression and pan-cancer as well as poor prognosis in humans, Jiang *et al.* (57) reported that METTL3 upregulation reduces the degradation rate of lncRNA SNHG1 in NSCLC. This particular RNA functions as a competing endogenous RNA that sponges miR-140-3p and increases the expression of UBE2C in lung squamous cell carcinoma (LUSC) cell lines (57). These findings suggest that METTL3 contributes to the function of the SNHG1/miRNA-140-3p axis, regulating UBE2C expression and NSCLC progression. Another study demonstrated that the coordination between METTL3 and YTHDC1 promotes the upregulation of circIGF2BP3 (58). This RNA then acts as a sponge for miR-328-3p and miR-3173-5p, which competitively increases the expression of *PKP3* (58). Subsequently, PKP3 interacts with the RNA-binding protein FXR1 to stabilize *OTUB1* mRNA (58). The resulting increase in OTUB1 facilitates PD-L1 deubiquitination, leading to $CD8^+$ T cell immune escape in patients with NSCLC, ultimately exacerbating the disease (58).

LncRNAs contain over 200 bases that do not code for proteins; however, they are linked to tumorigenesis and metastasis by serving as oncogenes or by interacting with target mRNAs, miRNAs and proteins (70,71). The functions of lncRNAs in NSCLC have been extensively reported; they are considered as risk factors for NSCLC that regulate the proliferation, metastasis, and immune resistance of NSCLC via interactions with METTL3 (72). For example, lncRNA ABHD11-AS1 is overexpressed in NSCLC tissues and cells; moreover, this overexpression is strongly correlated with an unfavourable NSCLC prognosis (59). Xue *et al.* (59) demonstrated that the upregulation of METTL3 caused the m^6A modification on ABHD11-AS1 to enhance its expression, which subsequently targeted and suppressed the expression of KLF4 (a cancer inhibitor), thereby promoting proliferation and the Warburg effect in NSCLC cells. These findings collectively suggest that ABHD11-AS1 might act as an oncogene in NSCLC tumorigenesis, which partially depends on the assistance of METTL3-mediated RNA m^6A modification. Similarly, Li *et al.* (60) revealed that increased expression of METTL3, together with YTHDF2, controlled the stemness and EMT features of LUAD cell lines by modulating the intrinsic levels of miR-146 and lncRNA TUSC7 by activating the Notch signalling pathway and targeting *Snail* mRNA. The lung cancer-associated transcript 3 (*LCAT3*), a novel oncogenic lncRNA, is overexpressed in LUAD; this overexpression correlates with poor prognosis (61). The upregulation of LCAT3 is attributed to m^6A modification facilitated by METTL3, which subsequently results in the stabilization of LCAT3 (61). Mechanistically, LCAT3 recruits far upstream element binding protein 1 (*FUBP1*) to the *MYC* far upstream element sequence, activating *MYC* transcription and promoting lung cancer cell proliferation, survival, invasion, and metastasis (61). Collectively, these oncogenic effects are achieved through the METTL3/LCAT3-FUBP1/FUSE axis.

The increased expression of lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) is associated with decreased survival in patients with NSCLC. Qi *et al.* (62) found that the abnormally increased expression of *NEAT1* was strongly linked to METTL3-mediated m^6A modification that stabilized NEAT1. This subsequently increased the expression of high-mobility group AT-hook 1 (HMGA1) by sponging miR-361-3p. Therefore, METTL3 triggered the signalling via the NEAT1/miR-361-3p/HMGA1 axis that functioned to promote NSCLC tumorigenesis and metastasis. Similarly, lncRNA deoxyguanosine kinase antisense RNA 1 (DGUOK-AS1) has been reported to be a driver in NSCLC. Feng *et al.* (63) found that the upregulation of DGUOK-AS1 promoted NSCLC metastasis indirectly by targeting *TRPM7* mRNA, which was regulated through METTL3/IGF2BP2-mediated m^6A modification.

The oncogenes in NSCLC are *c-MYC*, *METTL3*, and *LINC01006*. Liu *et al.* (64) found that c-MYC increased METTL3 expression, and METTL3 in turn functioned as an upstream regulator of LINC01006 via m^6A modification to stabilize LINC01006. Moreover, both c-MYC and LINC01006 functioned by targeting miR-34a/b/c and miR-2682 (64). This study indicated a positive feedback loop, with METTL3 as its central regulator. This provides another reason to explore the therapeutic targeting of METTL3 for NSCLC. Exosomes also have been found to increase the expression of METTL3. Xu *et al.* (65) demonstrated that M2 macrophage exosomal LINC01001 induced METTL3 expression, which, in turn, targeted *NASP* mRNA to alter glycolysis in NSCLC cells to promote NSCLC progression. Other lncRNAs that have been regulated by METTL3 in NSCLC include

LINC01833, which promotes NSCLC progression by regulating heterogeneous nuclear ribonucleoprotein A2/B1 expression (66); lncRNA DLGAP1 antisense RNA 2 promotes NSCLC aerobic glycolysis and tumorigenesis by regulating the YTHDF1/METTL3/c-Myc axis (67) (*Figure 3*).

In summary, recent investigations into the relationship between METTL3 and NSCLC collectively affirm that METTL3-mediated m^{6}A epigenetic modifications to RNAs play significant roles in the pathogenesis, development, and overall health status of NSCLC. Consequently, using METTL3 as a biomarker can possibly help in the clinical diagnosis and prognostic assessment of patients with NSCLC. Finally, targeting the regulation of METTL3 is a potential strategy for treating patients at multiple stages of NSCLC.

METTL3 is strongly associated with therapeutic resistance in NSCLC

The resistance of tumour cells to therapeutic drugs is a significant contributor to treatment failure. Besides its role in regulating cellular functions, METTL3 has been implicated in the modulation of therapeutic sensitivity in NSCLC.

METTL3 contributes to NSCLC chemoresistance

Chidamide, cisplatin, and gefitinib are usually used as the first-line drugs in NSCLC treatment. However, resistance is common during treatment. Ding *et al.* (73) found that chidamide upregulates the expression of METTL3 and WTAP, which subsequently promotes *c-MET* mRNA m^{6}A modification to increase c-MET expression and reduce sensitivity to crizotinib (a kinase inhibitor used for treating NSCLC with ALK mutations), in a c-MET/hepatocyte growth factor (HGF)-dependent manner. Furthermore, a separate study demonstrated that miR-4443 expression is elevated in exosomes derived from cisplatin-resistant NSCLC tumour tissues compared to those derived from cisplatin-sensitive tissues (74). This elevation inhibited cisplatin-induced FSP1-mediated ferroptosis *in vitro* and promoted tumour growth *in vivo* (74). Further mechanistic analyses revealed that miR-4443 regulates the expression of FSP1 through an m^{6}A-dependent mechanism involving METTL3, which has been identified as a direct target of miR-4443 (74). Additionally, increased METTL3 expression significantly correlated with susceptibility to cisplatin, more advanced tumour stage, nodal involvement, and lymph-node metastasis in NSCLC (75). This suggests that METTL3 plays a role in disease progression and chemoresistance by regulating *AKT1* mRNA m^{6}A levels to promote its expression (75). Similarly, study on the mechanism of cisplatin resistance in NSCLC cells has revealed that exosome-mediated circVMP1 promotes NSCLC tumour progression and resistance to cisplatin by targeting miR-524-5p-METTL3-SOX2 signalling (76). Therefore, targeting METTL3 also may be a viable therapeutic strategy for overcoming chemoresistance in NSCLC.

Gefitinib often leads to acquired drug resistance in patients with LUAD, resulting in treatment failure. Increased expression of small nucleolar host gene 17 (*SNHG17*) contributes to LUAD progression and gefitinib resistance by aggravating the malignant phenotypes (77). METTL3-mediated *SNHG17* m^{6}A modification stabilizes *SNHG17* transcripts and induces SNHG17 overexpression, which subsequently represses LATS2 expression by recruiting EZH2 to the promoter region of *LATS2* (77). Collectively, these findings suggest that METTL3 triggers the action of SNHG17/EZH2/LATS2 signalling in promoting gefitinib resistance. Additionally, gefitinib resistance induced by *EGFR* mutations is also regulated by METTL3-mediated m^{6}A modification. The EGFR-tyrosine kinase inhibitor (EGFR-TKI) gefitinib is the standard first-line therapy for patients with *EGFR* mutant NSCLC (78,79). However, acquired resistance often occurs during this treatment (80). Gao *et al.* (81) demonstrated that relative to gefitinib-sensitive tissues, METTL3 expression is increased in gefitinib-resistant tissues. Further mechanistic study has revealed that the combination of METTL3 and EMT gives rise to the activation of the PI3K/Akt signalling pathway, modulating gefitinib sensitivity (81). In line with this study, Dai *et al.* (82) indicated that LINC00969 regulated resistance to gefitinib by interacting with EZH2 and METTL3, transcriptionally regulating the level of H3K27me3 in the *NLRP3* promoter, and post-transcriptionally modifying the m^{6}A level of *NLRP3* in an m^{6}A-YTHDF2-dependent manner, thus epigenetically repressing NLRP3 expression to suppress the activation of classical NLRP3/caspase-1/GSDMD-related pyroptosis signalling, endowing an antipyroptotic phenotype, and promoting TKI resistance. Therefore, METTL3 can provide a molecular marker for predicting the efficacy of EGFR-TKI therapy and represents a potential therapeutic target. Liu *et al.* (83)

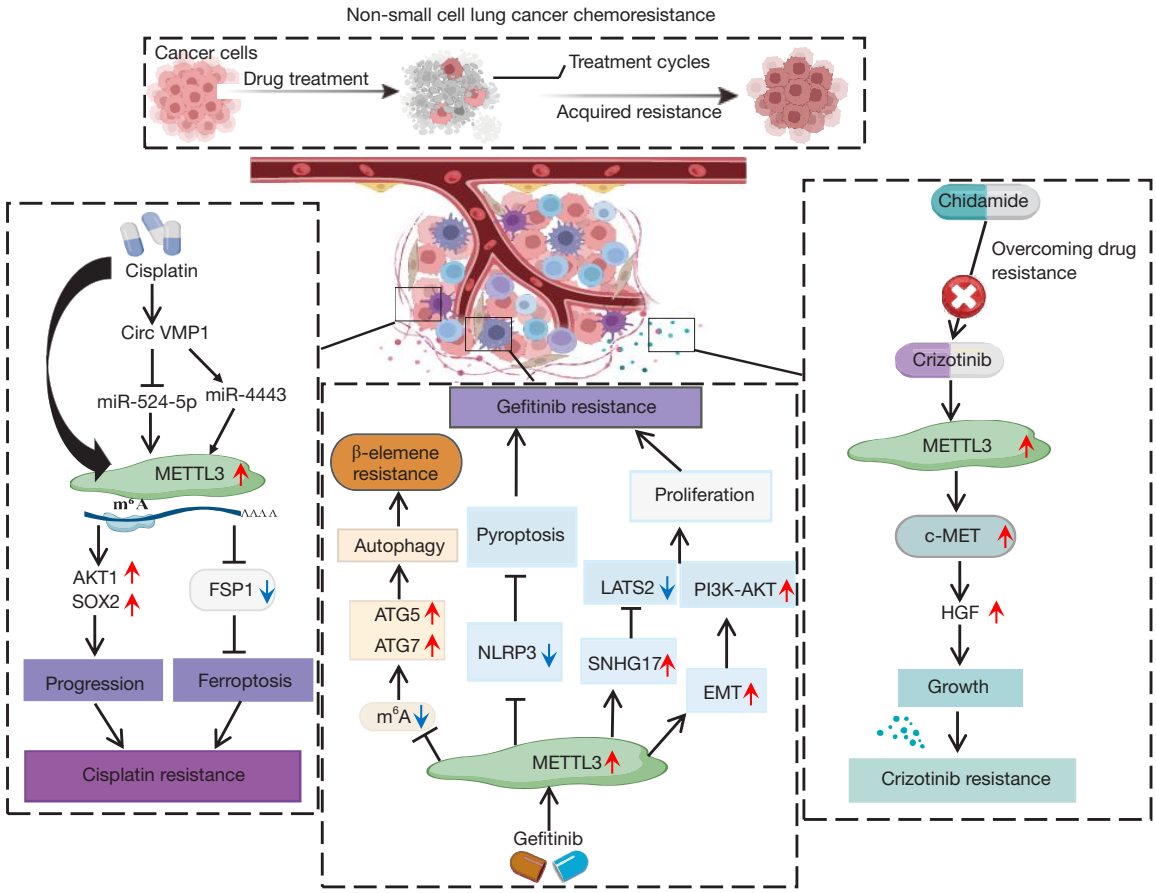

Figure 4 Upregulation of METTL3 induces chemoresistance in NSCLC. The targets, mechanisms, and outcomes of METTL3 in treating NSCLC are comprehensively summarised and analysed. Notably, resistance to chidamide, cisplatin, and gefitinib in NSCLC are closely associated with the upregulation of METTL3, which plays distinct roles and employs different mechanisms in these treatment-resistant events. Red arrows indicate the upregulated expression. Blue arrows indicate the downregulated expression. Black arrows indicate the "promote" function. NSCLC, non-small cell lung cancer; EMT, epithelial-mesenchymal transition.

demonstrated that METTL3-mediated autophagy plays a crucial regulatory role in reversing β-elemene resistance to gefitinib in NSCLC cells. Increased expression of METTL3 in LUAD tissues has been shown to reduce the methylation of RNA m^{6}A in drug-resistant cells, increase the expression of key autophagy pathway genes, including those that encode chelate 1, microtubule-associated protein 1b-light chain 3-II, autophagy-related genes (*ATG5* and *ATG7*), increasing β-elemene production, and ultimately reversing gefitinib resistance (83). These findings provide insights into additional potential targets for molecular therapy and NSCLC therapeutics for patients whose tumours are resistant to gefitinib (*Figure 4*).

METTL3 is strongly linked to NSCLC immunotherapeutic resistance

Immunotherapy has become the first-line treatment for advanced NSCLC, but most patients experience treatment failure (84,85). Interaction between PD-1 and PD-L1 drives resistance (86). METTL3 showed significant associations with the immune microenvironment, as well as tumour mutation burden and PD-L1 levels, suggesting that METTL3 mediated m^{6}A RNA methylation is indicative of therapeutic effects of anti-PD-L1 treatment (21,87). Sun *et al.* (88) reported that in NSCLC, METTL3/YTHDF2-mediated m^{6}A modification increased the expression of LINC02418, which subsequently interacted with *TRIM21*

mRNA to suppress PD-L1 expression and promote $CD8^+$ T cell infiltration. Therefore, the METTL3/YTHDF2-LINC02418-Trim21-PD-L1 axis contributes to NSCLC immunotherapeutic resistance. M2 phenotype tumour-associated macrophages (TAMs) are enriched in the tumour tissues of patients with immunoresistant LUAD (89,90). Wu *et al.* (91) found that M2-TAMs function to promote immunoresistance by increasing METTL3 expression and the total m^6A RNA level.

METTL3 functions in NSCLC radiotherapy resistance

Ionizing radiation is the standard radiation therapy for NSCLC; particularly carbon-ion radiotherapy, a radical nonsurgical treatment with high local control rates and rare serious adverse events (92,93). A recent study found that NSCLC cells developed resistance to carbon ion radiotherapy that might be due to METTL3-mediated m^6A modification. Xu *et al.* (94) showed that METTL3 expression was increased in NSCLC cells with carbon-ion radiotherapy, which modified H2A histone family member X (*H2AX*) mRNA to decrease its expression, reducing DNA damage repair and cell survival.

In summary, these studies demonstrate that METTL3-mediated RNA m^6A methylation plays a significant role in modulating therapeutic sensitivity in NSCLC, highlighting METTL3 as a potential predictor or target of resistance to chemotherapeutic drugs, immunotherapy, and radiotherapy.

Prospective clinical applications

Increased METTL3 expression in NSCLC tissues and advanced-stage lung cancers compared to adjacent tissues has been demonstrated (5). Furthermore, increased METTL3 expression triggers the onset and progression of NSCLC by modulating the expression for both coding and non-coding RNAs (5). Therefore, m^6A modification by METTL3 could be useful as prospective diagnostic or prognostic biomarkers for NSCLC (5). For example, Zhang *et al.* (95) tested FTO and METTL3 as prognostic biomarkers for evaluating benign and malignant tumours and predicting outcomes in patients with NSCLC. These studies also underscore the potential of downregulating METTL3 expression or regulating METTL3 targets in NSCLC treatment. Li *et al.* (96) recently reported that ammonium tetrathiomolybdate enhanced cell growth at low concentrations by increasing METTL3 expression in LUAD. Inhibition of METTL3 significantly attenuated proliferation by enhancing the expression of the eukaryotic translation initiation factor (eIF), underscoring the pivotal role of METTL3 in governing protein synthesis and cellular growth (96).

Currently, multiple methods have been reported for suppressing METTL3 expression in NSCLC treatment, for example, by using small-molecule inhibitors. As reported by Xiao *et al.* (97), STM2457, a small molecule, decreased METTL3 expression in NSCLC and increased PD-L1 expression, improving immunotherapy outcomes based on PD-L1 upregulation. Consistent with these data, Yu *et al.* (98) showed that the targeted regulation of METTL3 reprogramed the TME and improved immunotherapy. Interestingly, Du *et al.* (99) reported that miR-33a decreased the expression of METTL3 at both the mRNA and protein levels. They transfected miR-33a, targeting the 3'UTR of *METTL3* mRNA, and attenuated survival and proliferation of NSCLC cell lines (99). In addition, Wei *et al.* (100) demonstrated that transfection with miR-600 decreased expression of METTL3 and induced apoptosis in NSCLC cell lines (as evidenced by increased Bax/Bcl-2 ratios) via the PI3K/AKT pathway. Moreover, Huang *et al.* (101) found that METTL3 upregulation led to increased m^6A modification of miR-1246, promoting NSCLC progression by inhibiting the expression of paternally expressed gene 3 (*PEG3*). Conversely, knockdown of *METTL3* or overexpression of *PEG3* suppressed the malignant behaviour of NSCLC cells. Chen *et al.* (102) demonstrated that simvastatin treatment induced decreased expression of METTL3, which inhibited EMT progression through an IGF2BP2-dependent m^6A modification on the target *EZH2* mRNA (102). This suppressed the malignant characteristics of lung cancer, curbing further progression.

Besides inhibiting METTL3 directly for NSCLC treatment, targeting METTL3-regulated RNAs may be promising therapeutically. For example, metformin has been reported to improve the prognosis of patients with malignant tumours by inhibiting METTL3-mediated m^6A modification of *THRAP3*, *RBM25*, and *USP4* mRNAs to repress their expression, hamper cell proliferation, and promote apoptosis (103). Besides, Feng *et al.* (104) reported that decreasing expression of METTL3 by β-elemene attenuated the malignant behaviour of NSCLC by inhibiting phosphatase and tensin homolog (*PTEN*) mRNA degradation. RNA binding motif 10 (RBM10) is a potential tumour-suppressor protein that inhibits proliferation and promotes NSCLC apoptosis. Cao *et al.* (105) found that RBM10 functions as an RNA-binding protein that inhibits

Table 1 Downregulated METTL3 for NSCLC treatment

Inhibitor	METTL3		
	Target	Function	Reference
STM2457	*PD-L1*	Improve immunotherapy	(97)
miR-33a	*METTL3*	Attenuate proliferation	(99)
miR-600	*Bax/Bcl-2 ratio*	Induces apoptosis	(100)
PEG3	*miR-1246*	Inhibit malignant behaviour	(101)
Simvastatin	*EZH2*	Inhibit EMT progression	(102)
Metformin	*THRAP3, RBM25, USP4*	Hamper proliferation, promote apoptosis	(103)
β-elemene	*PTEN*	Malignant behaviour	(104)
RBM10	*MALAT1*	Inhibit proliferation, promote apoptosis	(105)
miR-1915-3p	*KLF4*	Impede migration, invasion, EMT	(106)

Downregulation of METTL3 directly or indirectly by different inhibitors rescues NSCLC via different targets and mechanisms. NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; EMT, epithelial-mesenchymal transition.

the m^{6}A methylation of *MALAT1* by recruiting METTL3 and altering phosphorylation of the downstream PI3K/AKT/mTOR pathway, ultimately inhibiting the invasion and migration of NSCLC by binding and regulating MALAT. Similarly, miR-1915-3p suppression significantly impedes migration, invasion, and EMT in NSCLC tissues and cell lines (106). Pan *et al.* (106) reported that METTL3/YTHDF2 signalling decreased miR-1915-3p levels through transcription factor KLF4, which directly binds to the 3'UTR of *SET* mRNA and modulates its expression via JNK/Jun and NF-kB signalling (*Table 1*).

In summary, elevated METTL3 expression plays a crucial role in NSCLC pathogenesis via diverse mechanisms and pathways. Therefore, METTL3 is a promising biomarker for the clinical diagnosis and prognosis of NSCLC. Moreover, downregulating METTL3 expression or regulating its targets may be effective by inhibiting cell proliferation and progression or inducing apoptosis.

Conclusions

Ongoing studies on m^{6}A modification show an increasing number of reports highlighting the role of METTL3 in regulating NSCLC. However, a comprehensive summary and analysis of the relevance and potential of METTL3 in the pathogenesis, clinical diagnosis, treatment, and prognosis of NSCLC are lacking. This review provides an updated summary of studies on METTL3 in NSCLC initiation, progression, chemoresistance, immunoresistance, and radioresistance and analysis their interrelationships, particularly their potential significance in clinical settings.

Our review analyzes how METTL3 contributes to the tumorigenesis and progression of NSCLC, especially LUAD, by regulating both mRNA and non-coding RNAs through distinct mechanisms. These include the regulation of cellular functions, including stemness, proliferation, migration, pyroptosis, autophagy, and apoptosis. Moreover, the mechanism of METTL3 action in NSCLC also involves the regulation of biological processes including the EMT, cell cycle, angiogenesis, TME, energy metabolism of the Warburg effect and glycolysis, immune escape, and immune microenvironment.

These data provide strong evidence to support the use of METTL3 expression as a promising biomarker for the diagnosis and prognosis of NSCLC. The downregulation of METTL3 may provide a potential therapeutic strategy for NSCLC treatment by inhibiting cell proliferation and progression or inducing cell death.

However, despite extensive research, we infer that current studies on METTL3 modifications in NSCLC are limited in their ability to explain the dynamic regulatory mechanisms involved in the onset and progression of these conditions. Although some studies have suggested that targeting METTL3-related regulatory factors and signalling pathways may have therapeutic potential for NSCLC, further large-scale clinical data are needed to support this hypothesis. Therefore, we propose some new avenues for future investigation. First, adenosine-to-inosine

(A-to-I) editing of RNA is a common RNA modification in mammals that is catalysed by adenosine deaminase acting on RNA (ADAR) enzymes (107). Several groups have indicated the interaction between METTL3 and ADAR-mediated RNA editing in multiple cancers, indicating that *METTL3* RNA is subject to RNA editing; moreover, METTL3 itself participates in RNA editing, e.g., in glioma (107). However, to the best of our knowledge, studies of the interaction between METTL3 and ADAR-mediated RNA editing in NSCLC are lacking. Therefore, exploring the interaction between METTL3 and ADAR-mediated RNA editing might be a novel perspective for understanding mechanisms of NSCLC pathogenesis. Second, although several methods have been reported to be effective in inhibiting METTL3 expression, exploring more specific methods with large-scale clinical data are needed for guiding more precise targeted therapies in clinical setting. Finally, the downstream targets of METTL3 need to be further identified and characterized, which will help us further understand the mechanism of METTL3 in NSCLC.

To sum up, this review has analysed the complex relationships between METTL3 and NSCLC, enhancing our understanding of its pathogenesis and treatment from a novel perspective of METTL3-mediated RNA m^6A modification, serving as a valuable reference for both research and clinical settings.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-85/coif). The authors have no conflicts of interest to declare.

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