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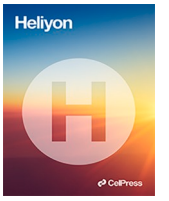

Review article

# Exploring the interplay between methylation patterns and non-coding RNAs in non-small cell lung cancer: Implications for pathogenesis and therapeutic targets

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ABSTRACT

Lung cancer is a global public health issue, with non-small cell lung cancer (NSCLC) accounting for 80–85 % of cases. With over two million new diagnoses annually, understanding the complex evolution of this disease is crucial. The development of lung cancer involves a complex interplay of genetic, epigenetic, and environmental factors, leading the key oncogenes and tumor suppressor genes to disorder, and activating the cancer related signaling pathway. Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNA (lncRNAs), and circular RNA (circRNAs) are unique RNA transcripts with diverse biological functions. These ncRNAs are generated through genome transcription and play essential roles in cellular processes. Epigenetic modifications such as DNA methylation, N6-methyladenosine (m6A) modification, and histone methylation have gained significant attention in NSCLC research. The complexity of the interactions among these methylation modifications and ncRNAs contribute to the precise regulation of NSCLC development. This review comprehensively summarizes the associations between ncRNAs and different methylation modifications and discusses their effects on NSCLC. By elucidating these relationships, we aim to advance our understanding of NSCLC pathogenesis and identify potential therapeutic targets for this devastating disease.

## 1. Introduction

Cancer is a global public health concern [1]. In the United States, it is predicted that there will be 1,918,030 new cases of cancer and 609,360 deaths in 2022; lung cancer accounts for approximately 350 cases each day and is the main reason for cancer-related death [2]. Among all the newly diagnosed cases, approximately 85 % were categorized as non-small cell lung cancer (NSCLC), thereby making it the most prevalent subtype of lung cancer [3]. Different factors affect the cell growth, development or cancer progression of NSCLC. For example, air pollution [4], diet [5], chronic diseases [6] and depression [7] can affect NSCLC with different pathological mechanisms [8]. The five years survival rate of NSCLC is low, standing at 15 % [9]. In this study, we specifically investigate the three main subtypes of NSCLC: squamous cell carcinoma (LUSC), adenocarcinoma (LUAD), and large-cell carcinoma (LCC) [10]. These

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subtypes were selected based on their prevalence and clinical significance, as they collectively represent the majority of NSCLC cases. Several studies show that a close association between epigenetic changes and the pathogenesis of NSCLC [11]. Three major epigenetic mechanisms involved in NSCLC include DNA methylation, RNA methylation, and histone modification [11]. These epigenetic patterns can alter visible phenotypes without altering the DNA sequence [12], while also regulating gene expression and maintaining genome stability [ [13,14]. Building upon previous studies, we found that the dysregulation of epigenetic mechanisms can contribute to the development of NSCLC [15].

### 1.1. DNA methylation (DNA methylation)

Catalyzed by the DNA methyltransferase family (DNMTS), DNA methylation comprises the transfer of a methyl group from S-adenosine methionine (SAM) to the fifth carbon position in the cytosine ring of the CpG dinucleotide, resulting in the formation of 5 mC [16]. DNA methylation plays a crucial role in gene regulation and cell differentiation [17,18]. Generally, DNA hypermethylation represses gene expression, leading to the silencing of important tumor suppressors or regulatory regions in the genome. This can result in dysregulation of cell proliferation or an altered response to cancer therapy [19]. However, DNA hypomethylation causes oncogene activation, chromosome misalignment during cell division, unnecessary activation of transposable elements in the genome, and loss of imprinting [20]. Aberrant DNA methylation patterns, particularly in gene-specific promoters, have been identified in lung cancer [21]. These aberrant DNA methylation patterns are believed to be involved in tumorigenesis [22]. Zhang et al. demonstrated that DIO3OS is silenced by DNA methylation and drives NSCLC progression by activating the hnRNPK-MYC-CDC25A axis [23].

### 1.2. N6-methyladenosine (m6A)

Among eukaryotic miRNAs, m6A is a most abundant modification. During the m6A modification, m6A methyltransferases catalyze the addition of m6A modifications to RNA molecules, while demethylases are responsible for the removal of m6A modifications [24]. Multiple methyltransferase complexes (MTC) catalyze m6A modification [25]. The key component of the m6A MTC is methylation transferase protein 3 (METTL3), which binds to S-adenosine methionine (SAM) [26]. Another important component, methyltransferase protein 14 (METTL14), is localized to the nuclear speck in a 1:1 ratio and composes a steady complex with METTL3 [27]. METTL3 plays a catalytic role, whereas METTL14 mainly stabilizes the MTC structure and recognizes specific RNA sequences as catalytic substrates [28]. Thus, M6A modification can occur by an m6A methyltransferase called a “writer,” be cleared by a demethylase called an “eraser,” and the “reader" m6A binding protein recognizes it [29]. The m6A modification is dynamic and reversible in mammalian cells [30]. These reversible processes are essential for cell viability, embryonic stem cell (ESC) differentiation, and various disease progressions, including cancer, as they modulate the biological function of cells [31].

### 1.3. Histone methylation

Histone methylation, first identified in 1960, is a common histone modification wherein methyl groups (-CH3) are added to lysine or arginine residues [32]. Histones H2A, H2B, H3, and H4, which are the core components of nucleosome subunits, can form octamers encircled by DNA fragments [33]. Histone methylation mainly occurs on the histone tail, specifically at the end of the lysine (K) and arginine residues (R) at the N-terminus [34]. Histone methylation is regulated by histone methyltransferases (HMT) and histone demethylases (HDM) [32]. HMTs can be classified into histone lysine methyltransferases (HKMT) and histone arginine methyltransferases (PRMT) [35]. Methylation of lysine (K) and arginine (R) residual in the histone tail mostly ascertains chromatin configuration and subsequent biological results [33]. HDMs can be divided into two families: KDM1/LSD1 (lysine demethylase 1 family) and Jumonji C (JmjC) domain-containing demethylases (JHDMs) [36]. LSD1 demethylates H3K4me1/2 and H3K9me1/2 based on the cellular environment [37]. However, the JmjC family of demethylases can remove lysine trimethylation modifications [38]. In lysine methylation, histone lysine methyltransferases (KMTs) act as “writers” of the histone code by adding methyl groups, while histone lysine demethylases (KDMs) act as “erasers” by removing methyl groups [39]. Some of the histone methylation modifier has set up a file in the active change of cancer was identified and exhibit either oncogenic or tumor suppressive properties [33,40]. Aberrations in histone methylation modifiers are also intimately related to lung cancer [41,42].Kuo et al. found that JARID1B/KDM5B, a histone demethylase, is a good prognostic predictor of NSCLC and promotes cancer aggressiveness [43].

### 1.4. Non-coding RNA (ncRNA)

Non-coding RNAs (ncRNAs) mainly constitute of microRNA (miRNAs), long non-coding RNA (lncRNAs), and circular RNA (circRNAs) [44]. miRNAs can regulate other RNA expression, especially mRNAs [44], by binding to complementary sequences at their 5′ end, loading one strand (the guide strand) of the miRNA double-strand to the Argonaute protein, and forming an RNA-induced silencing complex (RISC) consisting of a mature 22-nucleotide miRNA [45]. Although lncRNAs are RNA transcripts longer than 200 nucleotides, they don’t encode proteins, circRNAs are a subclass of long non-coding RNA with covalently linked ends [46]. Mature miRNAs combine with the 3′ untranslated region (3′ UTR) of mRNA, inhibiting translation or degradation [47]. miRNAs have a profound influence on downstream processes because over 60 % of the encoding genes are potential targets of miRNAs [48]. Unlike tsRNAs and piRNAs, miRNAs have been extensively studied in small ncRNA species associated with cancer [49]. Alterations in miRNAs have been observed in all types of cancer that have been studied [50]. It has been reported that miRNA can be involved in tumorigenesis by directly or indirectly targeting tumor suppressor genes or oncogenes [51](Fig. 1).

ncRNA host genes can transfer methyl groups to the C5 position of cytosine under the catalysis of DNMTS, forming 5-methylcytosine and completing the DNA methylation process. The subsequent development of DNA methylation varies with the degree of methylation. DNA hypermethylation can silence important tumor suppressor genes or regulatory regions, while DNA hypomethylation can lead to the activation of cancer genes and affect the process of cell proliferation. ncRNA host genes are transcribed to generate ncRNA. Under the action of m6A methyltransferase, m6A is modified to NcRNA to increase the methyl group, thereby regulating the expression and function of RNA, and m6A demethylase can remove methyl groups to reverse this process. Both of them form a dynamic and reversible process that affects cell growth and development and cancer progression. The histone parts of ncRNA host genes can also be methylated, which can be added by HMT or erased by HDM. After the host gene of ncRNA is modified by methylation, it can form mature ncRNA, such as miRNA, lncRNA, and circRNA, which enter the cytoplasm through the nuclear pore to play a role.

## 2. Correlation between methylation and miRNAs in NSCLC

Interactions between miRNAs and epigenetic pathways can form a miRNA-epigenetic feedback ring that affects gene expression and proliferation [52]. Disrupting the interaction between methylation modifications and miRNAs can prevent the progression of NSCLC [53]. Therefore, this section focuses on the associations between different types of methylation and miRNAs in NSCLC.

### *2.1. Correlation between DNA methylation and miRNAs*

#### *2.1.1. miRNAs are regulated by DNA methylation*

DNA methylation is closely associated with miRNA expression. Low methylation of CpG islands in the promoter can activate miRNA expression, whereas high methylation can inhibit miRNA transcription [54]. The hypermethylation of miR-148a-3p promoter reduced the expression of miR-148a-3p, negatively regulated the expression of mitogen-activated protein (MAP) kinase 9 (MAP3K9) in A549 and NCI–H1299 cells, obviously inhibited the growth, migration, invasion and cytoskeleton reorganization of LUAD, and inhibited epithelial-mesenchymal transition. Moreover, miR-148a-3p hypermethylation is closely related to lymph node metastasis [55]. Yang et al. proved that miR-203a-3p was lowered by promoter DNA hypermethylation and promoted the proliferation, migration, and invasion of NSCLC cells through indirect inhibition of DNA methyltransferase 3 B (DNMT3B), a directly goal of miR-203a-3p [56].

#### *2.1.2. Regulation of DNA methylation by miRNAs*

The DNMT family members, DNMT1, DNMT3A, and DNMT3B, maintain and establish DNA methylation [15]. The methylation state can affect miRNA expression, and this process is achieved through the binding of DNMT to cytosine residues and 5-methyl cytosine in the CpG island of the miRNA host gene promoter [57]. Similarly, miRNAs can inhibit the expression of DNMT, thereby

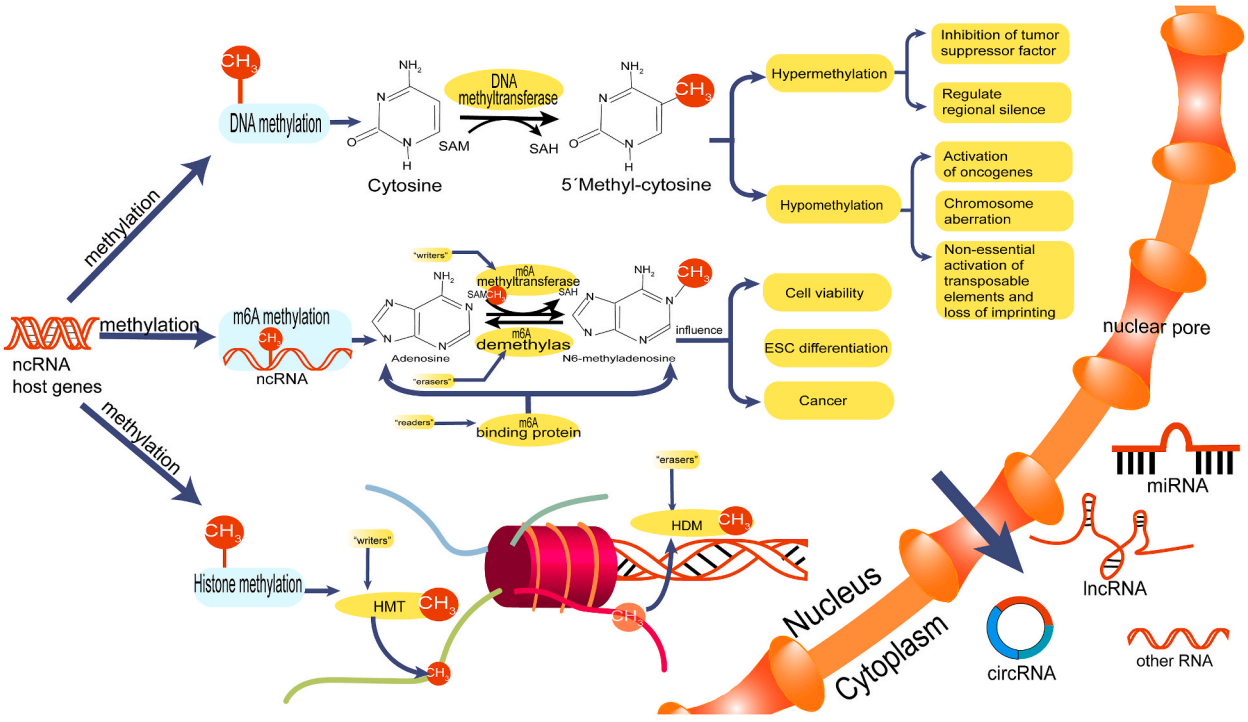


**Fig. 1.** The process and subsequent development of DNA methylation, m6A modification, and histone methylation of ncRNA host genes.

affecting the occurrence and development of NSCLC [58]. Yu et al. found that overexpression of miR-26a-5p negatively regulated the DNA methylation level of SFRP1 promoter by binding to DNMT3A, increased the expression of SFRP1, and inhibited the proliferation, clone formation and CSC-like properties of NSCLC cells [59].

### 2.2. Crosstalk between m6A and miRNAs

#### 2.2.1. MiRNAs are regulated by m6A

The m6A modification can affect the biogenesis or stability of miRNAs, thereby affecting the onset and progression of cancer [60]. METTL14 regulates miRNA processing and maturation through m6A modification [61]. METTL14 by modifying m6A adjust the miRNA processing and mature. METTL14-mediated m6A induces the recognition and pri-miR-19a was processed by DGCR8, promotes the transformation of pri-miR-19a to miR-19a-5p, inhibits the expression of RBM24 and reduces the binding to AXIN1 through the miR-19a-5p/RBM24/AXIN1 axis. Finally, inhibition of AXIN1 transcription enhances DDP resistance in NSCLC cells [62]. Therefore, disruptions in this process may promote further development of NSCLC or contribute to chemical resistance [63]. However, it has been found that the modification of m6A can regulate miR-21–5p and miR-107 and affect their target gene expression, thus weakening their ability to promote proliferation and movement, and inhibit tumor growth and metastasis [64,65]. On the contrary, m6A modification can regulate miRNA-140–3p and miR-21–5p to promote the invasion and metastasis of NSCLC, thus leading to poor prognosis [66,67].

#### 2.2.2. Regulation of m6A by miRNAs

The regulation of m6A by miRNAs is also a key mechanism affecting NSCLC progression [68]. Overexpression of miR-524–5p down-regulated the mRNA reflected by METTL3 and SOX2 protein expression in lung cancer chemotherapy-resistant cells A549/DDP and H1299/DDP, negative regulation of METTL3 and SOX2 gene protein expression levels in NSCLC cells and promoted the progression of NSCLC and the chemotherapy resistance of DDP [69]. Among them, METTL3 actively promotes the expression of m6A on such ncRNAs in NSCLC. Song et al. also demonstrated that exosomal miR-4443 overexpression promotes cisplatin resistance and FSP1m6A modification mediated iron death is modulated by METLL3 to enhance tumor growth in vivo NSCLC [69].

### 2.3. Crosstalk between histone methylation and miRNAs

Histone methylation facilitates or inhibits gene transcription. The position of the target amino acid and its methylation level indicate its complex functions in cancer [70]. miRNAs promote cancer cell apoptosis and anticancer drug resistance by regulating histone methylation [71]. Liu et al. found that the high expression of miR-409–3p can down-regulate the expression of antioxidant SOD1 in NSCLC cells through the miR-409–3p/SOD1/SETDB1 epigenetic regulation feedforward loop, induce NSCLC cell cycle arrest, and delay the progression of cancer [72]. Chen et al. also found that the histone H3K9 methyltransferase SET domain fork 1 (SETDB1) can directly be targeted by miR-29s, thereby negatively regulating H3K9 dimethylation and trimethylation levels and inhibiting NSCLC [73]. Histone methylation affects cancer progression by inducing autophagy [74]. Both H4K20me3 and the histone methyltransferase EHMT2 have been shown to reduce cell viability in NSCLC cell lines by inducing autophagy [75,76].

## 3. Crosstalk between methylation and lncRNAs in NSCLC

lncRNAs are RNA transcripts over 200 base pairs in length that reside in the cytoplasm or nucleus and do not encode proteins [77]. With the quickly development of high-throughput technique, more and more lncRNAs have been discovered, an increasing number of lncRNAs have been discovered. Previous studies have shown that lncRNAs affect the pathological and physiological processes of various human cancers [78]. For example, LINC00858 has abnormally high expression levels in NSCLC, colorectal carcinoma, pulmonary carcinoma, and other malignancies, promoting tumor occurrence and cancer development [79]. lncRNAs can regulate various subcellular processes, such as cell multiplication and death, thus participating in the development of many diseases [80,81]. Zheng et al. found that the effect between epigenetically regulated lncRNAs and DNA methylation played an essential role in the development of lung adenocarcinoma [82]. Variations in lncRNAs and epigenetic regulation are associated with cancer initiation and progression [83]. This section highlights the relationship between varied methylation types and miRNAs in NSCLC.

### 3.1. Crosstalk between DNA methylation and lncRNAs

#### 3.1.1. lncRNAs is regulated by DNA methylation

The crucial epigenetic mechanism regulating gene expression is DNA methylation [84]. DNA methylation affects the expression of lncRNAs by regulating the methylation level of their host gene promoters [85]. For example, the expression of lncRNA MIR503 HG in NSCLC organization was higher than that in para-carcinoma tissue. LncRNA MIR503HG promoter hypomethylation can inhibit the proliferation and migration of LUAD and promote tumor migration and invasion by down-regulating the expression of SNHG17 through the upstream regulatory axis lncRNA MIR503HG/SNHG17/miR-330–3p/regulating axes of prognostic inflammatory response-related genes (IRRGs). At the same time, SNHG 17 may be a biological marker for the diagnosis and prognosis of LUAD [86]. Therefore, DNA hypomethylation may play a key role in the development of NSCLC by regulating lncRNA MIR 503HG. On the other hand, increased DNA methylation can lead to decreased expression of lncRNA LCIIAR in LUAD, inhibit the metastasis of LUAD, and improve the prognosis of patients [87]. In addition, Sun et al. found that lncRNAs annotated in GENCODE (V28), CDO1-LNC, and their co expression genes were chiefly involved in DNA replication, cell cycle, and cell development. Their expression can be altered by DNA

methylation to control its expression and the host gene CDO1, thereby inhibiting the development of NSCLC [88].

#### 3.1.2. Regulation of DNA methylation by lncRNAs

lncRNAs can also affect the development of NSCLC by regulating DNA methylation. Studies have shown that overexpression of lncRNA ELF3-AS1 in NSCLC cells can lead to increased methylation of miR-212, down-regulate the expression of miR-212, and inhibit the role of miR-212 in cancer cell invasion and migration. At the same time, its high expression can predict the decline of NSCLC survival rate [89]. Kang et al. also demonstrated that the lncRNA MIR210HG could upregulate the methylation of the CACNA2D2 promoter by binding to DNMT2, relieving the retarding effect of CACNA2D2 overexpression on cell multiplication and promoting NSCLC proliferation and invasion [90]. The oncogenic lncRNA SNHG9 in glioblastoma overexpresses hypermethylated miR-21 in NSCLC and attenuates its enhanced effect on cancer cell proliferation [91]. Furthermore, sex influences the susceptibility to cancer [92]. TTTY15, a male-specific long non-coding RNA, interacts with DNA (cytosine-5) -methyltransferase 3A (DNMT3A). Knockdown of TTTY15 increases the binding of DNMT3A to the TBX4 promoter, inhibiting NSCLC occurrence and metastasis [93].

### 3.2. Crosstalk between m6A and lncRNAs

The m6A regulated protein METTL3 participates in the m6A modification of lncRNAs, thereby affecting the expression of their downstream target genes [94]. Li et al. found that METTL3-induced m6A methylation of the long non-protein coding RNA 1833 (LINC01833) promotes NSCLC progression by regulating the expression of the RNA-binding protein HNRNPA2B1 [95]. Xue et al.also discovery that m6A transferase METTL3 can enhance the stability of lncRNA ABHD11-AS1 transcripts, ectopic high expression promotes the proliferation of NSCLC and reduces the survival rate of patients [96]. In addition, m6A modifications can improve the stability of methylated lncRNAs in an m6A-dependent manner [97]. For example, m6A modification enhances the stability of the methylated SNHG1 transcript to upregulate SNHG1 in NSCLC, potentially regulating the expression of ubiquitin coupling enzyme 2C (UBE2C) through the METTL3/SNHG1/miRNA-140–3p axis, leading to a poor prognosis [66]. Yin et al. also showed that the lncRNA-RNA component of RMRP, mediated by m6A RNA methylation, is a highly upregulated lncRNA associated with poor NSCLC survival, which could promote cancer stem cell properties and epithelial-mesenchymal transition by increasing the stability of RMRP through RNA methylation. Thus, resistance to radiotherapy and cisplatin is enhanced [98].

### 3.3. Crosstalk between histone methylation and lncRNAs

Not only can lncRNAs be methylated by DNA and RNA, but they can also be methylated by histones [99]. On the one hand, lncRNAs can regulate histone methylation [100]. LINC00511 binds to the histone methyltransferase enhancer of zeste congener 2 (EZH2) and acts as a modular bracket for the EZH2/PPRC2 complex, specifying histone modification patterns on target genes, thereby changing the cell biology of NSCLC [101]. On the other hand, histone methylation in turn, can also regulate lncRNAs [102]. Arpita et al.'s study found that lysine methyltransferase 5c (KMT5C), as an epigenetic factor, can catalyze histone H4 lysine methylation (H4K20). Simultaneously, the deletion of KMT5C can upregulate the cancer long non-coding RNA LINC01510, which drives the development of resistance in NSCLC to a variety of epidermal growth factor receptor inhibitors (EGFRi), for instance erlotinib, afatinib, and osimertinib [103].

## 4. Crosstalk between methylation and circRNAs in NSCLC

CircRNAs are non-coding RNAs that have a covalent closed-loop conformation and are produced by reverse splicing of mRNA exons (pre-mRNA) [104]. CircRNAs are highly conservative and stable due to their counteract to RNase R [105]. CircRNAs regulate oncogenes interacting with RNA-binding proteins, sponging miRNAs, and regulating protein translation [106]. CircRNAs also play an important role in DNA methylation and regulation of m6A modification [107]. Therefore, the crosstalk between methylation and circRNAs in NSCLC is discussed in this section.

### 4.1. Crosstalk between DNA methylation and circRNAs

#### 4.1.1. Association between DNA methylation and circRNAs

CircRNAs can regulate downstream target genes of DNA methylation and promote cancer development [108]. Zhao et al. discovered that CircTFF1 could promote BCL3B promoter methylation via the miR-6c-29p/DNMT3A axis, downregulate BCL6B's inhibitory effect on the malignant behavior of lung cancer cell lines, and thus promote pulmonary carcinoma cell proliferation, migration, and invasion [109]. Circernashsa _ CIRC _ 0077,837 was also shown to be up-regulated in NSCLC cells and inhibits apoptosis by increasing its genomic methylation to downregulate phosphatase and tensin homolog (PTEN) [110]. Similarly, Chen et al. found that overexpression of CircMMP11 hypermethylated miR-143, down-regulation of miR-143 expression weakened its inhibition of circMMP11 and enhanced cell proliferation. Moreover, overexpression of CircMMP11 can predict low survival rate [111].

#### 4.1.2. Regulation of circRNAs by DNA methylation

CircRNAs can also be controlled by DNA methylation, which, in turn, affects circRNA expression [112]. Pre-NOL10 methylation and epithelial splicing regulatory protein 1 (ESRP1) regulates circNOL10 expression. circNOL10 can affect mitochondrial function by inhibiting cell proliferation and cell cycle progression, and it can promote lung cancer cell apoptosis by regulating the human protein

polypeptide family and affecting a variety of signaling pathways [113].

### 4.2. Crosstalk between m6A and circRNAs

CircRNAs also play a vital role in the adjustment of m6A modifications [114]. On the one hand, m6A has the ability to regulate circulation. Xu et al.reported that YTHDF2 can positively adjust the decomposition of m6A-modified circ _ SFMBT2, thereby enhancing the proliferation and metastasis of NSCLC cells [115]. On the other hand, circRNAs can regulate m6A modifications. circRNAs tonoplast 1 (circVMP1) and circNOTCH1 have been shown to promote cell growth and cancer progression in NSCLC cells by regulating m6A modifications [116,117].

## 5. Other ncRNAs

In addition to the aforementioned ncRNAs, siRNAs, piRNAs, and housekeeping RNAs can crosstalk via methylation [118–120]. Studies have shown that siRNAs targeting EHZ2 can silence the expression of EHZ2 mRNA and protein. Downregulation of EHZ2 expression can increase A549/DDP and AGS/DDP cell methylation, effectively reversing cisplatin resistance in human lung cancer cells, inhibiting proliferation, and improving cisplatin resistance [121]. Amaar et al. found that the overexpression of RASSF1C and knockdown of RASSF1C and PIWIL1 in genomic regions regulated DNA methylation and that RASSF1C-PIWI-piRNA is involved in cancer and acts as a tumor suppressor gene, regulating the occurrence and development of lung cancer stem cells [122]. Different types of housekeeping RNAs can interact with each other and are associated with methylation [123]. Wang et al. found that SNORD88C in small nucleolar RNA (snoRNA) can promote 28′-*O*-methylation at C3680 on 2*S* rRNA, which in turn enhances downstream SCD1 translation, inhibits autophagy, and promotes growth and metastasis of NSCLC [124](Fig. 2 and Fig. 3).

(a) Correlation between DNA methylation and miRNAs; (b) Crosstalk between m6A and miRNAs; (c) miRNAs regulates histone methylation; (d) Crosstalk between DNA methylation and lncRNAs; (e) Crosstalk between m6A and lncRNAs; (f) Crosstalk between histone methylation and lncRNAs; (g) Crosstalk between DNA methylation and circRNAs; (h) siRNAs regulates DNA methylation; (i) piRNAs regulate DNA methylation.

DNA methylation can be di-vided into hypermethylation and hypomethylation. The host gene of miRNAs can be transcribed to form the primary transcript product, pri-miRNAs, which is modified to form the precursor miRNAs, pre-miRNAs, and then passes through the nuclear pore to the cytoplasm to form the mature miRNAs. The expression of miRNAs varies with the degree of DNA methylation. Hypermethylation inhibits the expression of the miRNAs gene, while hypomethylation activates the expression of miRNAs. The final mature miRNAs were bound to Argonaute protein, forming RISC and exerting their roles.

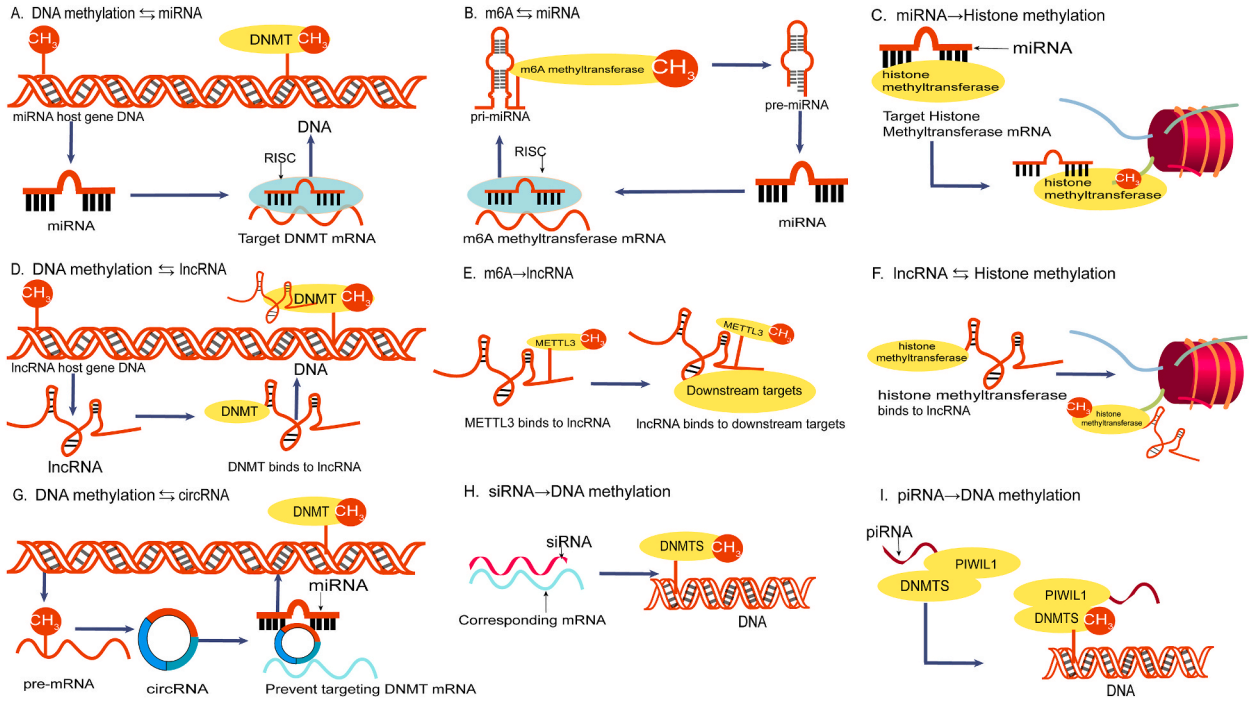


**Fig. 2.** Crosstalk between various methylations and ncRNAs.

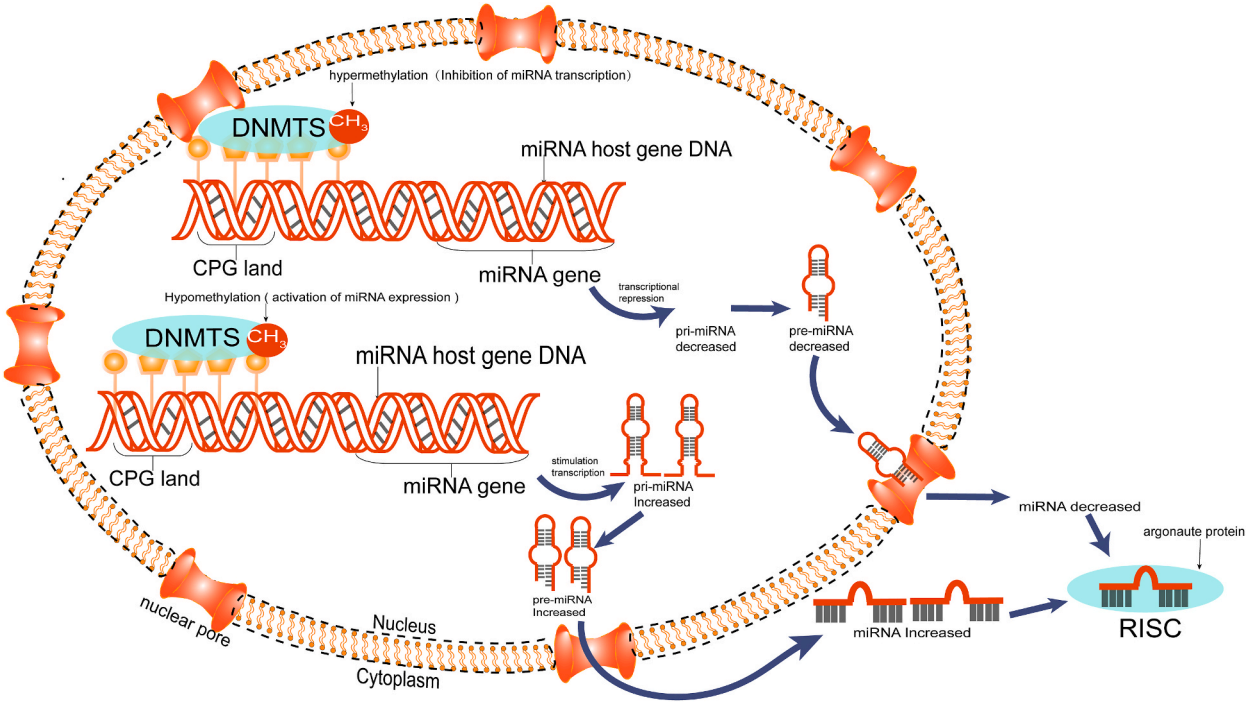


**Fig. 3.** DNA methylation progression of miRNAs.

## 6. Treatment and diagnosis

### 6.1. Diagnostic markers

In terms of diagnosis and treatment, this paper is based on the crosstalk between methylation and ncRNA, which interacts with each other to affect the occurrence and development of NSCLC. Therefore, both methylation and ncRNA can be considered as a diagnostic marker. First, methylation in NSCLC could be used as a possible marker [125]. Li et al. reported protein kinase Cδ-binding protein (PRKCDBP) as a potential tumor suppressor, and its promoter methylation level could be used as a latent marker for the primitive detection of NSCLC [126]. SCARA5, also known as TESR, is a scavenger receptor class A member 5 (SCARA5) expressed in various tissues and organs and is involved in host defense [127]. Studies have shown that SCARA5 expression is downregulated in lung cancer cell lines and tissues, and its level was negatively related to promoter methylation, thereby making it a novel methylation biomarker [128]. MLL2 histone methyltransferase is a tumor suppressor coded by the *KMT3C* gene. KMT2C promoter methylation can be used as an NSCLC biomarker in the plasma-free DNA (cfDNA) cycle for epigenetic biomarkers. The detection of KMT2C promoter methylation in plasma cfDNA can predict surgical safety, tumor metastasis, and prognosis in patients with NSCLC [129]. The DNA methylation/TMPO-AS1/let-7b-5p axis mediates high HMMR expression in LUAD, and HMMR is regarded as a biological marker for predicting the prognosis of LUAD [130]. JMJD2s belong to the histone demethylase family and are potential therapeutic targets to overcome NSCLC resistance [131]. Second, ncRNAs can be used as diagnostic markers [132]. Some studies have found that platelet-derived circRNAs are potential biomarker candidates for NSCLC progression and can be used as novel blood biomarkers for NSCLC detection [133].

### 6.2. Targets for treatment

Similarly, for the treatment of NSCLC, ncRNAs can be used as therapeutic targets [134]. For example, miR-26A1 is a key regulatory factor and potential therapeutic target for NSCLC. It can be used as a tumor suppressor to inhibit the proliferation and metastasis of NSCLC cells [135]. Oncogenes and methyltransferases can be used as therapeutic targets in NSCLC [136]. TdT interaction factor 1 (TdIF1) is expressed in NSCLC genes [137]. LSD1 raised promoter regions to adjust *E*-cadherin transcription, promote EMT and tumor metastasis, and is associated with poor prognosis; thus, TdIF1 can be used as a potential therapeutic target for NSCLC [138]. Methyltransferase-like 3 (METTL3) is an RNA methyltransferase that promotes the evolution and chemical resistance of NSCLC by regulating AKT1 mRNA m6A levels and promoting AKT1 protein expression. It also provides an effective therapeutic target to overcome chemotherapy resistance of NSCLC [139]. Eukaryotic histone methyltransferase 2 (EHMT2 or G9A) participates in the stemness of lung cancer by maintaining the epigenetic mechanism of DNA methylation and expression of multiple lung cancer stem cell genes and can be used as a potential therapeutic target for NSCLC [140].

### 6.3. Drug resistance

Drug resistance is inevitable in cancer treatment [141]. In NSCLC, certain therapeutic targets can suppress drug resistance in cancer cells, thus improving the treatment plan for NSCLC [142]. For cisplatin resistance, overexpression of nicotinamide nucleotide-transferase (NNT) in A549/DDP cells reduces cisplatin resistance and inhibits cell proliferation and colony formation [143]. However, certain targets also enhance cisplatin resistance [144]. METTL14 inhibits NSCLC cell proliferation and enhances apoptosis. METTL14 promotes apoptosis and inhibits the proliferation of NSCLC cells. However, METTL14-mediated m6A modification through the miR-19a-5p/RBM24erAXIN1 axis can promote the counteraction of NSCLC cells to DDP [145]. Exosome-transmitted circVMP1 promotes NSCLC progression and cisplatin counteraction by targeting the miR-524-5p-METTL3/SOX2 axis [116]. Furthermore, resistance to other drugs, such as m6 methyltransferase METTL3, mediates autophagy in NSCLC cells, which plays a vital role in the reversal of gefitinib resistance by β-elemene [146]. Jumonji C-domain-containing histone lysine demethylases (Jumonji KDMs) can augment paclitaxel sensitivity of NSCLC cells by inhibiting APC/CDH1-dependent degradation of CtIP and PAF15, which is promoted by Jumonji KDMs [147](Fig. 4).

(a) The promoter DNA methylation of PRKCDBP, SCARA5, KMT2C, and HMMR can change their expression in lung cancer cell lines and tissues, which can be used as new biomarkers for the diagnosis of NSCLC; (b) Histone methylation of JMJD2s inhibits JMJD2, which reduces the chroma-tin association between ATR and Chk1, inhibits the ATR-Chk1 replication checkpoint, and increases sensitivity to cisplatin; (c) The circRNAs contained in platelets in human blood can be used as a diagnostic marker for NSCLC; (d) ncRNAs, oncogenes, and methyltransferases can transform normal human lung cells into non-small cell lung cancer, so they can be used as potential therapeutic target; (e) NNT can reduce cisplatin resistance in NSCLC, while METTL14 and circVMP1 can increase cisplatin resistance. METTL3 can reverse gefitinib resistance. KDMs can increase the sensitivity of NSCLC cells to paclitaxel.

## 7. Future development

Up to now, epigenetic research on non-small cell lung cancer is still a hot research direction. However, there is no systematic and complete summary about the crosstalk between non-small cell lung cancer and methylation. In this review, the interaction between ncRNA and DNA methylation, m6A modification and histone methylation is summarized, which affects the occurrence and development of non-small cell lung cancer. Methylation mainly affects the expression of ncRNA from the host gene promoter methylation, m6A methylation and histone methylation modification during the formation of ncRNA. For ncRNA, it affects the progress of methylation by regulating methylation-related enzymes to add or erase methyl groups. In addition, we also found that methylation modification can be used as a potential diagnostic marker for non-small cell lung cancer, and methyl-related enzymes can also be considered as therapeutic targets. It also shows that methylation-related enzymes can also be used as a factor affecting drug resistance of non-small cell lung cancer. It is of great significance for the treatment of non-small cell lung cancer, which helps us to understand the

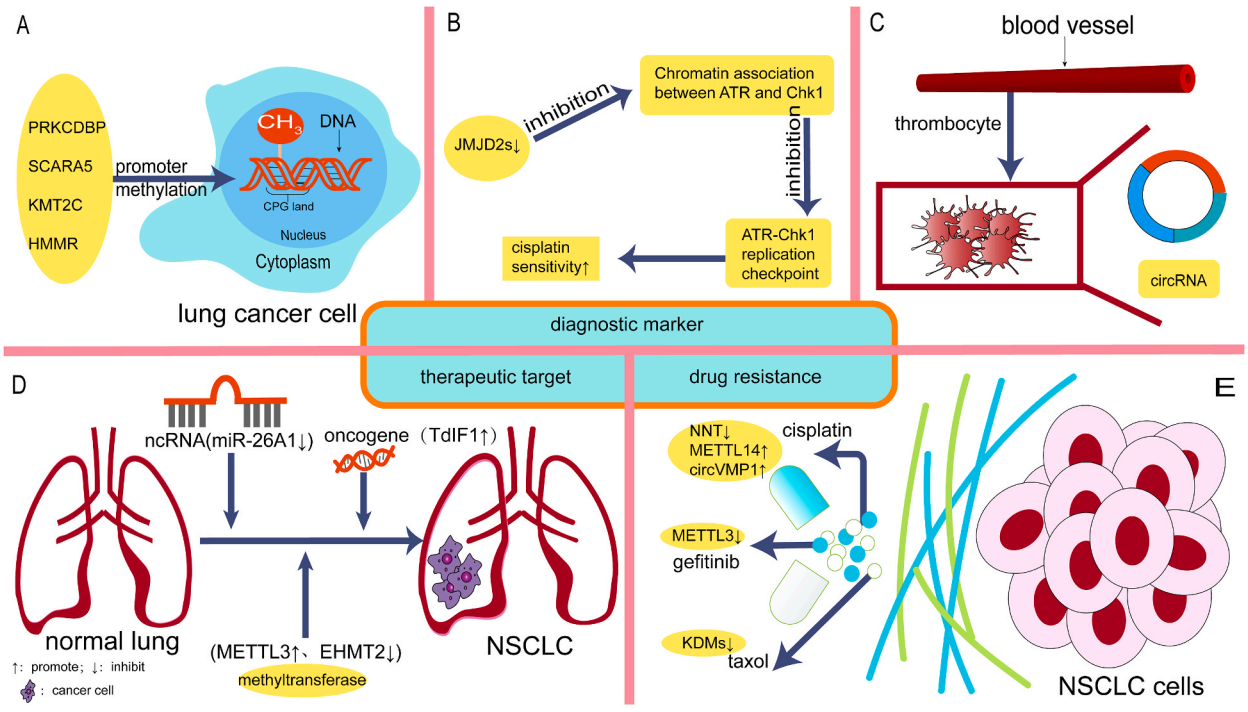


**Fig. 4.** Diagnosis and treatment of NSCLC.

complex crosstalk pattern between methylation and ncRNA more systematically and deeply and understand the specific mechanism of its influence on non-small cell lung cancer and provides a new idea for exploring the influence of epigenetics on non-small cell lung cancer, diagnostic markers and drug resistance treatment in the future.

## 8. Limitations and advantages

At present, there are still some limitations in this paper. First, the availability and quality of data. When selecting the literature, the article focuses on the strength of its correlation with this article. However, due to the current lack of reference data on the crosstalk between ncRNA and methylation in NSCLC, there are still few reference data even if the requirements for article quality are reduced. Secondly, for the role of methylation, some methylation types with less research on NSCLC in the existing published literature are not enough to form a summary text, so they are not shown in the article. In addition, this study also has certain advantages. We have made a comprehensive analysis of the selected literature, which has strong logic, critically shows the evidence, systematically and comprehensively summarizes the relationship between NSCLC and ncRNA and fills the gap in this respect.

## 9. Summary

Methylation plays an important role in cancer progression. The coaction between ncRNAs and methylation can accelerate cell multiplication, cancer cell transfer, drug resistance, autophagy, and other malignant behaviors that favor the progression of non-small-cell tumors. Epigenetic regulation can predict the likelihood of NSCLC and can be considered as a new diagnostic marker for early cancer development. Additionally, the epigenetic regulation of ncRNAs can serve as a treatment target for the treatment of NSCLC. Resistance to NSCLC treatment can be attributed to epigenetic regulation. However, it is important to note that these statements are summaries and analyses of preliminary research findings and further research is required to solidify these conclusions.

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## Data availability statement

No data was used for the research described in the article.

## CRediT authorship contribution statement

**Mei Yang:** Writing – original draft, Visualization, Methodology, Investigation. **Xue Hu:** Writing – review & editing, Writing – original draft, Software. **Bin Tang:** Writing – review & editing, Funding acquisition. **Fengmei Deng:** Writing – review & editing, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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