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The interaction between ncRNAs and the EGFR signaling pathway in lung cancer

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Highlights:

- EGFR and its downstream signaling pathways.
- Interplay between non-coding RNAs and the EGFR pathway in lung cancer.
- Non-coding RNAs involved in the regulation of EGFR-TKI resistance.

Abstract: EGFR mutations serve as a pivotal driver in NSCLC, where their aberrant activation promotes tumor proliferation, metastasis, and survival through downstream signaling pathways. Although EGFR-TKIs effectively target mutant EGFR, acquired resistance significantly diminishes their clinical efficacy. Recent studies have demonstrated that ncRNAs play a critical role in the dynamic regulatory network of the EGFR signaling pathway and are deeply implicated in the development of EGFR-TKI resistance in lung cancer. This review focuses on the dynamic bidirectional regulatory mechanisms between ncRNAs and the EGFR signaling pathway, as well as the multifaceted molecular mechanisms through which ncRNAs mediate resistance to EGFR-TKI therapy. Elucidating the interaction network between ncRNAs and the EGFR pathway not only provides novel molecular insights into resistance mechanisms but also establishes a theoretical foundation for developing ncRNA-based combination therapeutic strategies and dynamic biomarkers for monitoring resistance evolution, highlighting significant translational and clinical potential.

Keywords: ncRNA; EGFR signaling pathway; EGFR-TKI resistance; lung cancer

1. Introduction

Lung cancer is one of the most prevalent and deadly malignancies worldwide, posing a serious threat to human health. According to statistics, there were approximately 2.5 million new cases of lung cancer globally in 2022, accounting for 12.4% of all new cancer cases, while the number of lung cancer deaths reached 1.8 million, representing 18.7% of all cancer-related deaths [1].

Non-small cell lung cancer (NSCLC) is the predominant type of lung cancer, comprising over 85% of all cases [2]. Among NSCLC cases, epidermal growth factor receptor (EGFR) gene mutations are one of the key driving factors, particularly in Asian populations, where the EGFR mutation rate is notably high. In China, EGFR mutations are present in more than 50% of NSCLC patients [3]. Targeted therapy with EGFR tyrosine kinase inhibitors (EGFR-TKIs) has brought significant survival benefits to NSCLC patients with EGFR mutations. However, the emergence of drug resistance has gradually become a major limitation, hindering long-term efficacy and prompting researchers to explore new regulatory mechanisms [4].

In recent years, the role of non-coding RNAs (ncRNAs) in tumorigenesis, progression, and drug resistance has garnered increasing attention [5]. Major ncRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), among others, which play crucial roles in gene expression regulation and are involved in lung cancer development, metastasis, and drug resistance [6]. With deepening research on the interaction between the EGFR signaling pathway and ncRNAs, accumulating evidence suggests that ncRNAs may regulate the EGFR pathway through various mechanisms, influencing lung cancer drug resistance [7]. Nevertheless, studies on how ncRNAs systematically regulate the EGFR pathway and drug resistance in lung cancer remain in early stages. This review aims to comprehensively summarize the mechanisms by which ncRNAs regulate the EGFR pathway and drug resistance in lung cancer, with the goal of providing new insights and potential targets for precision therapy.

Nevertheless, studies on how ncRNAs systematically regulate the EGFR pathway and drug resistance in lung cancer remain in early stages. This review systematically summarizes the interaction mechanisms between ncRNAs and the EGFR pathway, and proposes a comprehensive regulatory network model. This model integrates the interactions between various key ncRNAs and EGFR, as well as its major downstream signaling pathways (Figure 1). In this regulatory network, EGFR serves as a critical node in signal transduction, subject to multi-level regulation by multiple non-coding RNAs. Some miRNAs, such as miR-146a-5p, can directly regulate EGFR expression by targeting EGFR mRNA [8]. In contrast, certain ncRNAs, including lnc-MLETA1 and Circ_0001955, indirectly modulate EGFR through their function as ceRNAs that bind to target miRNAs [9,10]. Additionally, the glycolysis-related lncRNA AL355338 enhances the stability of ENO1 and its interaction with EGFR, thereby activating downstream EGFR signaling pathways [11]. Some ncRNAs indirectly influence pathway activity by regulating downstream effector molecules of EGFR. For example, studies have shown that miR-19b directly targets PPP2R5E, thereby modulating and integrating the three major branches of the EGFR signaling pathway [12]. Notably, ncRNAs not only regulate the EGFR pathway but are also regulated by EGFR. EGFR further influences cancer progression by upregulating oncogenic ncRNAs and downregulating tumor-suppressive ncRNAs. For instance, EGFR with activating mutations can upregulate the levels of the well-known oncogenic ncRNA, miR-21 [13,14]. Additionally, feedback loops play a crucial role in this regulatory network. Studies have shown that

EGFR can activate the expression of miR-7 through the Ras/ERK/Myc signaling cascade, while exogenous overexpression of miR-7 leads to a reduction in EGFR expression levels. This negative feedback mechanism precisely regulates cellular fate [15]. Furthermore, there are also positive feedback regulations between ncRNAs and EGFR. For example, EGFR promotes the overexpression of circRNA C190 via the MAPK/ERK pathway, and the overexpressed C190 further enhances the phosphorylation of EGFR downstream ERK1/2, thereby promoting malignant progression in tumor cells [16]. In addition, this review further summarizes the mechanisms by which ncRNAs contribute to drug resistance in lung cancer, aiming to provide new insights and potential targets for the precise treatment of lung cancer.

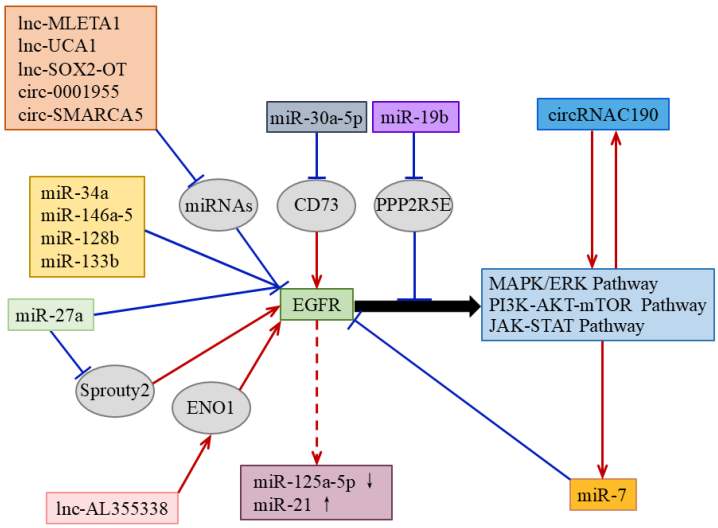

Figure 1. Crosstalk between EGFR signaling pathway and ncRNAs.

This schematic diagram briefly summarizes the interactions between ncRNAs and the EGFR signaling pathway. In the diagram, solid red arrows indicate promoting effects, blue lines with a short perpendicular line at the end represent inhibitory effects, and dashed red arrows denote regulatory effects. Within this regulatory network model, ncRNAs interact with the EGFR pathway through several mechanisms: (a) directly targeting EGFR mRNA, (b) binding to miRNAs that target EGFR mRNA or upstream proteins in the EGFR pathway, (c) binding to proteins that regulate EGFR activity, (d) double-negative regulation, (e) targeting regulatory proteins downstream of the EGFR pathway, (f) feedback loops, and (g) being regulated by mutated EGFR pathways. These interactions form a complex regulatory system involving the EGFR pathway.

2. EGFR signaling pathway in lung cancer

EGFR, a cell-surface tyrosine kinase receptor, is crucial for regulating the growth and metastasis of NSCLC via its signaling pathway [17]. As a key member of the receptor tyrosine kinase family, EGFR activates multiple downstream signal transduction pathways, thereby regulating tumor cell proliferation, survival, migration, and angiogenesis.

2.1. Structure of EGFR

EGFR, a 170 kDa transmembrane glycoprotein encoded by the EGFR gene (chromosome 7p12), functions as a tyrosine kinase receptor [18]. Structurally, EGFR contains three main regions: an

extracellular ligand-binding domain, a transmembrane region, and an intracellular kinase domain [19]. The extracellular region is the ligand-binding domain, comprising approximately 620 amino acid residues, which can be further divided into four subdomains (I–IV). Subdomains I and III are responsible for ligand binding, while subdomains II and IV are rich in cysteine residues and participate in dimerization. The transmembrane domain consists of 23 hydrophobic amino acids, serving as an anchoring structure connecting the extracellular and intracellular regions [20]. The intracellular region possesses tyrosine kinase activity, which can be further divided into the juxtamembrane region, the tyrosine kinase domain, and the C-terminal tail. The tyrosine kinase domain is the core region for EGFR signal transduction. Upon activation, it catalyzes the phosphorylation of specific tyrosine residues on itself or downstream substrates [21]. The C-terminal tail contains multiple autopho sphorylation sites. Upon phosphorylation, these sites act as docking points for adaptor proteins, thereby triggering downstream signaling pathways.

2.2. Activation of EGFR and its downstream signaling pathways

The activation of EGFR is a tightly regulated multi-step process. In its resting state, EGFR predominantly exists as a monomer on the cell membrane. Ligand binding induces conformational changes in the receptor, exposing dimerization interfaces that facilitate homodimerization or heterodimerization [22]. Dimerization triggers autophosphorylation of tyrosine residues within the intracellular kinase domain, thereby activating kinase activity. Phosphorylated tyrosine residues in EGFR's C-terminal tail recruit adaptor proteins containing SH2 or PTB domains (e.g., Grb2, Shc), enabling the recruitment of downstream signaling molecules and initiation of diverse transduction cascades [23]. In addition to ligand-dependent activation, EGFR can also be activated through ligand-independent mechanisms, including receptor overexpression, gene mutations, or epigenetic alterations. In tumor cells, these abnormal activation mechanisms often lead to sustained EGFR signaling, promoting tumorigenesis and progression [24].

2.2.1. MAPK/ERK sgnaling pathway

The MAPK/ERK pathway, the most classical downstream signaling pathway of EGFR, promotes cell cycle progression and gene transcription [25]. In lung cancer, abnormal activation of this pathway is closely associated with enhanced tumor cell proliferation and invasion [26]. The EGFR signaling cascade initiates when Grb2's SH2 domain engages phosphorylated EGFR residues, recruiting SOS to the plasma membrane. SOS catalyzes RAS activation by exchanging GDP for GTP. GTP-bound RAS then stimulates RAF kinase activity, initiating a phosphorylation cascade through MEK1/2 to ERK1/2. The activated ERK1/2 dimer translocates to the nucleus where it phosphorylates transcription factors including members of the AP-1 complex (c-Fos/c-Jun) and Elk-1, modulating expression of genes involved in cell proliferation and survival [27].

2.2.2. PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR pathway is another key downstream signaling pathway of EGFR, primarily associated with cell survival and anti-apoptosis. Its overactivation suppresses tumor cell apoptosis and promotes proliferation [28]. After EGFR activation, PI3K is recruited either directly or through adaptor

proteins, catalyzing the conversion of PIP2 to the second messenger PIP3. PIP3 serves as a membrane anchor, recruiting AKT and PDK1 to the cell membrane. PDK1 and the mTORC2 complex sequentially phosphorylate AKT, leading to its full activation. Activated AKT exerts broad biological effects by phosphorylating multiple downstream target proteins (e.g., BAD, GSK3β, FOXO, mTOR). Activated AKT exerts broad biological effects by phosphorylating multiple downstream targets (e.g. BAD, GSK3β, FOXO, mTOR) [29].

3. Interplay between non-coding RNAs and the EGFR pathway in lung cancer

3.1. miRNA and the EGFR pathway

miRNAs are small ncRNAs approximately 22 nucleotides (nt) in length that primarily regulate gene expression by binding to the 3' untranslated region (3'UTR) of target mRNAs, leading to translational repression or mRNA degradation [30]. The biogenesis of miRNAs involves transcription by RNA polymerase II into primary miRNA (pri-miRNA), which is then processed by the Drosha/DGCR8 complex into precursor miRNA (pre-miRNA). Subsequently, Exportin-5 transports pre-miRNA to the cytoplasm, where Dicer cleaves it into mature miRNA. The mature miRNA is finally incorporated into the RNA-induced silencing complex (RISC) to regulate target genes [31].

3.1.1 miRNAs directly targeting EGFR

miRNAs can directly inhibit the expression of EGFR by binding to the 3'UTR of EGFR mRNA.

Li *et al.* discovered that miR-34a expression is significantly downregulated in NSCLC tissues and cell lines. Their research demonstrated that miR-34a directly targets EGFR, thereby inhibiting cell proliferation, promoting apoptosis, and suppressing tumor growth and metastasis in NSCLC [32].

Qi *et al.* revealed that EGFR is a direct target of miR-146a-5p. Their study demonstrated that cryptotanshinone, a tanshinone compound derived from *Salvia miltiorrhiza*, suppresses NSCLC cell proliferation and cell cycle progression by upregulating miR-146a-5p expression, thereby inhibiting EGFR mRNA and protein levels. These findings suggest that both cryptotanshinone and miR-146a-5p hold promise as potential therapeutic candidates for NSCLC treatment [8].

Moreover, Weiss *et al.* demonstrated that miR-128b specifically regulates EGFR expression by targeting 3'UTR of EGFR mRNA, and Liu *et al.* demonstrated that miR-133b inhibits its translation by targeting the 3'-UTR of EGFR mRNA, playing a role in suppressing the malignant phenotype of NSCLC cells [33,34]. The discovery of these miRNAs directly targeting EGFR provides potential molecular targets for precision treatment strategies based on the EGFR signaling pathway.

3.1.2 miRNAs indirectly targeting EGFR

miRNAs can regulate the EGFR pathway not only by directly targeting EGFR mRNA but also by indirectly targeting upstream proteins of EGFR.

Zhu *et al.* observed that miR-30a-5p expression is downregulated in NSCLC tissues and cell lines, whereas CD73 is upregulated. Further experiments confirmed that miR-30a-5p inhibits CD73 expression by directly binding to its 3'-UTR, thereby suppressing NSCLC cell proliferation. Notably, in CD73-knockdown cells, the levels of EGFR and EGF-induced p-EGFR, as well as p-AKT

expression, were significantly lower than those in control cells. The miR-30a-5p-CD73-EGFR-AKT signaling axis offers a potential mechanistic explanation for NSCLC carcinogenesis and highlights novel therapeutic targets [35].

3.1.3 miRNA with dual regulatory mechanisms

Acunzo *et al.* uncovered a dual regulatory mechanism by which miR-27a modulates EGFR expression in NSCLC. On one hand, miR-27a directly binds to the 3'UTR of EGFR mRNA to exert post-transcriptional repression. On the other hand, miR-27a indirectly suppresses EGFR by targeting Sprouty2, a protein that positively regulates EGFR through attenuation of ubiquitination-mediated degradation, thereby stabilizing EGFR protein. In NSCLC cellular models, their study validated that miR-27a overexpression significantly reduces Sprouty2 levels, while Sprouty2 silencing decreases EGFR expression, collectively establishing dual negative regulation of the EGFR signaling axis [36].

3.1.4 miRNA regulated by EGFR

miRNAs regulate EGFR and its pathway proteins directly/indirectly, while also mediating EGFR-triggered gene cascades, revealing a bidirectional miRNA-EGFR interplay.

Baumgartner *et al.* found that miR-19b can regulate and integrate the three major branches of the EGFR signaling pathway (ERK/STAT/AKT). Experiments confirmed that overexpression of miR-19b significantly enhances the phosphorylation levels of ERK1/2, AKT, and STAT, while inhibition of miR-19b reduces EGFR pathway activity. The mechanism involves miR-19bdirectly targeting and suppressing the expression of the serine/threonine phosphatase PP2A regulatory subunit PPP2R5E, thereby controlling downstream EGFR signaling. In EGFR-mutant NSCLC, miR-19b cooperates with EGFR to drive cell proliferation, migration, and apoptosis resistance. This mechanism reveals that the PP2A-PPP2R5E complex acts as a central hub for miR-19b-dependent comprehensive regulation of multiple signaling pathways [12].

Wang *et al.* identified miR-125a-5p as a downstream target of the EGFR signaling pathway, whose expression is significantly suppressed by EGFR activation. This suppression was reversed upon treatment with the tyrosine kinase inhibitor gefitinib. *In vitro* experiments showed that knockdown of miR-125a-5p in PC9 cells led to downregulation of miR-125a-5p, which markedly enhanced malignant phenotypes, including accelerated proliferation, increased angiogenic capacity, and heightened migratory/invasive properties. Furthermore, among 15 analyzed lung cancer samples, one-third exhibited significant downregulation of miR-125a-5p. These findings strongly suggest that miR-125a-5p is negatively correlated with lung cancer metastasis and likely functions as a tumor suppressor during disease progression [37].

Seike *et al.* demonstrated that EGFR with activating mutations significantly upregulates miR-21 levels. Pharmacological inhibition of EGFR signaling using the tyrosine kinase inhibitor AG1478 markedly suppressed miR-21 expression. Combined treatment of H3255 and H441 cells with AG1478 and anti-miR-21 synergistically elevated caspase-3/7 activity, thereby promoting apoptotic processes [14].

In Chou *et al.*'s study, the dual regulatory mechanism and molecular basis of miR-7 in lung cancer progression were elucidated. As a canonical oncomiR, miR-7 expression is regulated by the EGFR pathway: EGFR activates its transcription via the Ras/ERK/Myc signaling cascade, where c-Myc

directly binds to the miR-7 promoter to enhance transcriptional activity. Functionally, miR-7 targets the coding sequence of Ets2 repressor factor (ERF), reducing ERF protein levels and alleviating its suppression of cyclin A. This mechanism drives tumor cell proliferation and enhances *in vivo* tumorigenic capacity. Notably, in CL1-5 cells, while EGFR stimulation upregulated miR-7, exogenous miR-7 overexpression not only suppressed ERF but also induced compensatory downregulation of EGFR. This observation suggests a negative feedback loop within the EGFR-miR-7-ERF signaling axis, where dynamic equilibrium governed by homeostatic regulatory networks may determine ultimate cell fate. Such precise regulatory interplay could underlie the context-dependent phenotypic switching of miR-7, which exhibits both oncogenic and tumor-suppressive roles across distinct tumor microenvironments [15].

3.2. lncRNA and the EGFR pathway

LncRNAs are a class of ncRNAs longer than 200 nt that regulate gene expression through mechanisms such as chromatin remodeling, transcriptional interference, or acting as miRNA sponges [38]. Typically transcribed by RNA polymerase II, many lncRNAs undergo splicing and 5’ capping modifications. They exert regulatory functions by interacting with DNA, RNA or proteins [39].

3.2.1 lncRNA as a miRNA sponge

lncRNAs can act as miRNA sponges, binding to miRNAs and thereby preventing them from inhibiting their target genes. Hsu *et al.* identified lnc-MLETA1, a long non-coding RNA upregulated in highly metastatic lung cancer cells and their secreted exosomes. Mechanistically, lnc-MLETA1 acts as a sponge for miR-186-5p and miR-497-5p, thereby derepressing EGFR and insulin-like growth factor 1 receptor (IGF1R) expression. The SOX2-OT/miR-345-5p/EGFR ceRNA regulatory axis drives lung cancer cell motility and metastasis. Their findings highlight lnc-MLETA1 as a critical mediator of metastatic progression and a potential diagnostic biomarker or therapeutic target for lung cancer [9].

Fu’s team investigated the molecular mechanisms of PM2.5-induced malignant transformation in bronchial epithelial cells. They found that environmental particulate matter (e.g. PM2.5) significantly upregulates lncRNASOX2-OT. This lncRNA competitively binds to miR-345-5p, alleviating its inhibitory effect on EGFR, thereby forming a SOX2-OT/miR-345-5p/EGFR competing endogenous RNA (ceRNA) regulatory axis. Activation of this network drives EGFR overexpression, promoting malignant transformation and enhancing the proliferative and migratory capacities of bronchial epithelial cells. This discovery elucidates a novel epigenetic pathway linking environmental pollutants to lung cancer, providing a theoretical basis for molecular surveillance and targeted intervention in PM2.5-associated lung cancer [40].

LncRNAs can not only regulate the expression of EGFR by binding to miRNAs that target EGFR, but also by interacting with miRNAs targeting other members of the epidermal growth factor receptor family, thereby promoting the malignant phenotype of lung cancer cells. In Nie *et al.*’s study, lncRNA-UCA1 was found to be upregulated in NSCLC tissues and demonstrated oncogenic functions. This effect is partially mediated by its interaction with miR-193a-3p, which leads to the upregulation of ERBB4 (a miR-193a-3p target gene), thereby promoting NSCLC cell proliferation [41].

3.2.2 lncRNA as a protein binder

In addition to binding miRNAs, lncRNAs can also interact with proteins, thereby regulating the stability and function of the proteins. Hua *et al.* revealed that AL355338, a glycolysis-associated lncRNA, is elevated in NSCLC and enhances tumor aggressiveness. AL355338 directly binds to α-enolase (ENO1), stabilizing ENO1 protein and strengthening its interaction with EGFR. This interaction triggers EGFR/AKT signaling cascade activation, driving invasive phenotypes. The study proposes the AL355338-ENO1-EGFR/AKT axis as a promising therapeutic target for NSCLC [11].

3.3. circRNA and the EGFR pathway

CircRNAs are covalently closed RNA molecules with high stability. They primarily function as miRNA sponges or protein scaffolds to modulate cellular processes [5]. circRNAs are formed through back-splicing, lacking a 5' cap and 3' poly(A) tail. They regulate signaling pathways by sequestering miRNAs or binding to proteins [42].

3.3.1 circRNA as a miRNA sponge

CircRNA can bind to miRNAs targeting EGFR, thereby alleviating their inhibitory effect on EGFR expression. Ding *et al.* revealed that Circ_0001955 was significantly overexpressed in NSCLC tissues and cell lines, with its expression level positively correlated with advanced tumor TNM stage and lymph node metastasis. Functionally, overexpression of Circ_0001955 promoted cell proliferation and suppressed apoptosis. Mechanistically, Circ_0001955 directly binds to and inhibits miR-769-5p, thereby alleviating the negative regulation of miR-769-5p on its target gene EGFR. This interaction activates the EGFR signaling pathway, driving malignant phenotypes in NSCLC and establishing a "Circ_0001955/miR-769-5p/EGFR" signaling axis. These findings suggest Circ_0001955 as a potential therapeutic target for intervening in the imbalance between tumor proliferation and apoptosis [10].

SMARCA5 is a highly conserved chromatin remodeling factor. CircSMARCA5, derived from exons of the SMARCA5 gene, functions as a molecular sponge for miR-17-3p [43]. Geng *et al.* demonstrated that miR-17-3p directly targets EGFR mRNA, leading to downregulation of EGFR expression. Silencing circSMARCA5 induced EGFR downregulation and played a critical role in the progression and metastasis of lung adenocarcinoma through the circSMARCA5-miR-17-3p-EGFR-cMyc/p21 axis. This regulatory network highlights the therapeutic potential of targeting circSMARCA5 to disrupt oncogenic signaling cascades in lung cancer [44].

3.3.2 Feedback-regulated circRNA

Ishola *et al.* revealed that circRNAC190 was significantly overexpressed in both NSCLC clinical specimens and cell lines. Mechanistically, the EGFR signaling pathway drives C190 overexpression via MAPK/ERK-dependent transcriptional regulation. Transient or stable overexpression of C190 promoted ERK1/2 phosphorylation, cell proliferation, and migration *in vitro*, while accelerating xenograft tumor growth *in vivo*. Through database predictions and experimental validation, C190 was identified as a ceRNA that sponges miR-142-5p, thereby derepressing its downstream targets CDK1 and CDK6. By integrating the EGFR-MAPK-ERK axis with cell cycle regulation, C190 establishes a

pro-tumorigenic feedback loop. Targeted inhibition of C190 may offer a novel therapeutic strategy to disrupt this oncogenic signaling cascade in lung cancer [16].

The ncRNAs mentioned in this chapter are summarized in Table 1.

Table 1. The ncRNAs interacting with EGFR signaling pathway mentioned in this review.

ncRNA	Crosstalk with EGFR Pathway	Reference
miR-34a	Directly targeting mEGFR	[32]
miR-146a-5p		[8]
miR-27a		[36]
miR-128b		[33]
miR-133b		[34]
miR-30a-5p	Indirectly inhibiting EGFR by targeting CD73 mRNA	[35]
miR-19b	Inhibiting EGFR downstream signaling pathways by targeting PPP2R5E	[12]
miR-125a-5p	Regulated by EGFR	[37]
miR-21		[14]
miR-7		[15]
lnc-MLETA1	Indirectly inhibiting EGFR by sponging miRNA	[9]
lnc-SOX2-OT		[40]
lnc-AL355338	Indirectly activating EGFR signaling pathway by binding to ENO1	[11]
circ-C190	Regulated by EGFR	[16]
circ-0001955	Indirectly inhibiting EGFR by sponging miRNA	[10]
circ-SMARCA5		[44]

4. Non-coding RNAs in EGFR-TKI drug resistance mechanisms

4.1. Mutation types of EGFR and targeted therapeutic agents

Mutations in the EGFR gene are one of the critical drivers of lung cancer, particularly NSCLC [45]. Common EGFR mutations predominantly occur in the tyrosine kinase domain, including the exon 19 deletion mutation and the exon 21 L858R point mutation [46], accounting for approximately 45% and 40% of all EGFR mutations, respectively. These mutations induce conformational changes in the EGFR protein, resulting in constitutive activation of its tyrosine kinase activity and subsequent persistent activation of downstream signaling pathways [47]. The aberrantly activated signaling pathways inhibit tumor cell apoptosis and promote uncontrolled proliferation and metastasis [17]. The aberrantly activated signaling pathways inhibit tumor cell apoptosis and promote uncontrolled proliferation and metastasis [48]. The T790M mutation is a major mechanism of acquired resistance to EGFR-TKIs, observed in approximately 60% of patients with acquired resistance [49]. This mutation occurs at the

"gatekeeper" residue within the EGFR tyrosine kinase domain, reducing the binding affinity of EGFR to first- and second-generation EGFR-TKIs, thereby conferring drug resistance [50].

Targeted therapeutic agents against EGFR primarily include EGFR-TKIs and monoclonal antibodies [51]. Here, we focus exclusively on EGFR-TKIs. EGFR-TKIs competitively inhibit the tyrosine kinase activity of EGFR, blocking the activation of downstream signaling pathways and suppressing tumor cell proliferation and survival [52]. First-generation EGFR-TKIs, such as gefitinib and erlotinib, reversibly bind to EGFR, inhibiting its tyrosine kinase activity, reducing autophosphorylation of its dimer, and interrupting intracellular signaling [53]. Second-generation EGFR-TKIs, including afatinib and dacomitinib, irreversibly inhibit the tyrosine kinase activity of EGFR and act on multiple targets, suppressing signaling through all homodimers or heterodimers of the ErbB/HER family [54]. Third-generation EGFR-TKIs (e.g., osimertinib, rociletinib) selectively target T790M mutations, showing superior efficacy and reduced side effects *versus* earlier generations in EGFR-mutant patients [55].

4.2. Primary resistance ncRNAs

Primary resistance ncRNAs are a class of non-coding RNA molecules that intrinsically contribute to the ability of cells (e.g., cancer cells) to resist therapeutic interventions prior to exposure to treatment. These ncRNAs mediate resistance mechanisms through regulatory roles in key cellular processes.

MiR-7 can target multiple sites in the 3'-untranslated region of EGFR mRNA. The plasmid expressing miR-7 suppresses the proliferation and tumor formation of EGFR-TKI-resistant lung cancer cells both *in vitro* and *in vivo* [56]. Exosome-derived miR-7 can transfer from sensitive cells to T790M-mutant resistant cells, activating Hippo pathway signaling transduction by targeting the Yes-associated protein (YAP) mRNA 3'-UTR, ultimately reversing gefitinib resistance [57].

TGFβ-mediated suppression of the miR-200 family leads to upregulated expression of mitogen-inducible gene 6 (MIG6), which subsequently negatively regulates EGFR. Additionally, TGFβ induces tumor cell transition to an epithelial-mesenchymal transition (EMT)-associated kinase state characterized by AKT-activated EGFR-independent status, thereby generating EGFR TKI-refractory EGFR-independent mesenchymal phenotypes. The MIG6/miR200 ratio shows positive correlation with erlotinib resistance [58]. Zinc finger E-box binding homeobox-1 (ZEB1) acts as a transcriptional repressor to inhibit miR-200c transcription, thereby promoting its target NOTCH1 while suppressing ERBB3 promoter activity and expression to inhibit cell growth [59].

MiR-199a-3p/5p exerts tumor-suppressive effects in NSCLC by targeting Ras homolog enriched in brain (Rheb) to inhibit mTOR signaling, thereby suppressing tumor growth, metastasis, and drug resistance. Its overexpression enhances gefitinib sensitivity in EGFR-T790M mutant NSCLC, with reduced expression observed in clinical samples and databases [60].

Let-7c enhances gefitinib sensitivity in H1975 cells by suppressing RAS expression, consequently inhibiting PI3K/AKT and MEK/ERK signaling pathways [61].

MiR-590 increases erlotinib sensitivity by targeting the 3'-UTR of EHD1 (an Eps15 homology domain-containing protein), leading to EHD1 downregulation, while being suppressed by upstream NF-κB [62].

AXL, a member of the Tyro-AXL-Mer receptor tyrosine kinase family, marks mesenchymal-like EGFR-TKI-resistant cells. Reduced intracellular miR-335 promotes AXL-positive cell generation and enhances erlotinib resistance [63].

MiR-486-5p inhibits NSCLC cell growth, migration, and resistance by targeting the 3'-UTR of proto-oncogene Pim-1. Co-downregulation of miR-486-5p with eIF4E upregulation in NSCLC promotes Pim-1 overexpression and gefitinib resistance [64].

The lncRNA APCDD1L-AS1 reverses the transcriptional repression of SIRT5 by sponging miR-1322/miR-1972/miR-324-3p, thereby inhibiting autophagic degradation of EGFR, upregulating its expression and activation, and driving icotinib resistance [65].

Studies indicate that loss of lysine methyltransferase 5C (KMT5C) leads to LINC01510 upregulation. LINC01510 promotes transcription of the oncogene MET, driving multidrug resistance in NSCLC [66].

4.3. Acquired resistance via EMT

In cancer therapy, tumor cells can develop resistance to drugs through various mechanisms. One significant mechanism is the acquisition of resistance via EMT. EMT is a biological process in which epithelial cells gradually lose their polarity and tight cell-cell junctions, transforming into mesenchymal-like cells with increased migratory and invasive capabilities. This transformation allows tumor cells to evade the effects of targeted therapeutic agents, leading to treatment failure. In recent years, ncRNAs have been found to regulate the expression of EMT-related genes, thereby promoting the occurrence of EMT.

Studies demonstrate that miR-200c enhances gefitinib sensitivity in PC-9-ZD (gefitinib-resistant cell line) by inducing apoptosis and proliferation inhibition through PI3K/Akt pathway suppression, while targeting ZEB1 to inhibit EMT progression and cell migration [67]. Similar results were observed through miR-200c overexpression in erlotinib-resistant A549 lung adenocarcinoma cells [68].

MiR-205 depletion induces erlotinib resistance in EGFR-mutated NSCLC cells. CRIPTO1 (also called teratocarcinoma-derived growth factor 1) activates Src tyrosine kinase and ZEB1 to downregulate miR-205, inducing EMT-mediated primary resistance to EGFR-TKIs [69].

LncRNA BC is overexpressed in LUAD cells. By participating in the regulation of alternative splicing of inositol monophosphatase domain containing 1 (IMPAD1), it generates distinct transcript variants, which cooperatively induce the EMT process, thereby enhancing resistance to gefitinib [70].

4.4. Bypass signaling and compensatory activation

In addition to acquiring drug resistance through EMT, bypass signaling and compensatory activation are also important pathways of drug resistance in tumor cells. Bypass signaling refers to the activation of alternative signaling pathways by tumor cells when the primary pathway is inhibited by drugs, allowing them to maintain their proliferation and survival capabilities. NcRNAs not only closely interact with EGFR but also have extensive crosstalk with other receptor tyrosine kinases and other signaling axes. Through interactions with human epidermal growth factor receptor 2 (HER2), hepatocyte growth factor receptor (MET), as well as signaling pathways such as Wnt and Hippo, ncRNAs regulate drug resistance in lung cancer cells within a broader network context. Compensatory

activation, on the other hand, occurs when certain signaling molecules or pathways exhibit enhanced activity in response to drug treatment instead of being fully suppressed. Recent studies have shown that ncRNAs play multidimensional roles in regulating these resistance mechanisms.

In EGFR-mutated lung adenocarcinoma, low miR-630 expression positively correlates with gefitinib resistance. Specifically, reduced miR-630 elevates its target protein YAP1, thereby promoting ERK activation. This process further enhances transcriptional suppression of miR-630, forming a feedback loop that sustains low miR-630 expression. The persistent ERK pathway activation through the miR-630/YAP1/ERK feedback loop induces phosphorylation and degradation of the pro-apoptotic protein Bad, conferring TKI resistance [71].

MiR-147b shows significant upregulation in osimertinib-tolerant EGFR-mutated lung cancer cells. By targeting Von Hippel-Lindau (VHL), a tumor suppressor protein, miR-147b activates pseudo-hypoxic responses and targets SDHD, a subunit of the succinate dehydrogenase complex, thereby inhibiting SDH enzymatic activity, disrupting the tricarboxylic acid cycle, and ultimately establishing osimertinib resistance [72].

MiR-204 substantially enhances lung cancer cell sensitivity to osimertinib through BIM upregulation and caspase activation, intensifying drug-induced apoptosis. Additionally, it suppresses cancer stemness and EMT by targeting CD44, thereby attenuating cell migration and invasion [73].

TGF-β1 induces overexpression of miR-134, miR-487b, and miR-655 in EMT-exhibiting lung adenocarcinoma cells by directly targeting Membrane-Associated Guanylate Kinase, WW and PDZ Domain Containing 2 (MAGI2), promoting both EMT progression and gefitinib resistance [74].

MiR-146b-5p was found to be significantly downregulated in EGFR TKI-resistant cells. miR-146b-5p inhibits EGFR TKI resistance by targeting IRAK1, suppressing nuclear factor κB (NF-κB) activity and NF-κB-related IL-6 and IL-8 production [75].

MiR-33a overexpression exerts tumor-suppressive effects by negatively regulating ATP-binding cassette subfamily B member 7(ABCB7) and 70 kDa ribosomal protein S6 kinase 1(p70S6K1). In resistant cells, Histone deacetylase 1(HDAC1) upregulation cooperates with Forkhead box K1(FOXK1) to silence miR-33a expression, enhancing gefitinib resistance [76].

Research found that miR-139-5p enhances sensitivity to gefitinib by suppressing the expression of Bone Morphogenetic Protein 4 (BMP4) in drug-resistant cells, thereby affecting Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4) and the tumor suppressor gene p53, which indirectly regulates cellular energy metabolism. In gefitinib-resistant NSCLC cells, miR-139-5p is significantly downregulated [77].

Erlotinib-induced EGFR inhibition downregulates miR-21, resulting in increased stability of Tumor Necrosis Factor (TNF) mRNA, a target of miR-21. TNF activates the transcription factor NF-κB, which in turn enhances the transcription of TNF mRNA. This augmented pro-survival signaling ultimately contributes to the development of drug resistance [78].

MiR-483-3p rescues EMT phenotypes in gefitinib-resistant EGFR-mutant NSCLC by directly targeting integrin β3 to inhibit FAK/Erk signaling, thereby markedly attenuating cellular migration, invasion, and metastatic capacity [79].

MiR-34a suppresses cell growth and induces apoptosis in EGFR-mutant NSCLC by targeting MET, overcoming HGF-induced MET/PI3K/Akt pathway activation and gefitinib resistance [80].

The long non-coding RNA SNHG14 is upregulated in gefitinib-resistant NSCLC tumor tissues and cells. It sponges miR-206-3p, thereby alleviating the inhibitory effect of miR-206-3p on ABCB1 expression. ABCB1, a critical member of the ATP-binding cassette (ABC) transporter superfamily, primarily mediates the transmembrane efflux of chemotherapeutic drugs through ATP hydrolysis-dependent energy supply, directly influencing intracellular drug accumulation efficiency. Overexpression of SNHG14 promotes cell viability, reduces apoptosis, enhances colony-forming capacity, and increases resistance to gefitinib [81].

LncRNA H19 is downregulated in erlotinib-resistant EGFR-mutant lung cancer cells, thereby diminishing its induction of ubiquitin-mediated degradation of Pyruvate Kinase M2 (PKM2). The upregulated PKM2 enhances AKT phosphorylation, which promotes the development of erlotinib resistance [82]. Furthermore, H19 has been shown to reduce the expression of glutathione peroxidase 4 (GPX4) in H1975 and H1650 cell lines, thereby promoting cellular ferroptosis and consequently enhancing their sensitivity to erlotinib [83].

Erlotinib treatment significantly induces lncRNA SOX2-OT overexpression. lncRNA SOX2-OT promotes erlotinib resistance by enhancing the expression of EGFR pathway components AKT/ERK, increasing AKT phosphorylation [84].

Lnc00665 is significantly upregulated in NSCLC tissues and cells with acquired gefitinib resistance. By interacting with Enhancer of zeste homolog 2 (EZH2), lnc00665 activates the PI3K/AKT signaling pathway, thereby promoting the activation of EGFR and its downstream effector AKT, ultimately inducing acquired resistance to gefitinib [85]. EZH2, a core subunit of Polycomb Repressive Complex 2 (PRC2), is a key epigenetic regulatory protein. LncRNA CASC9, another long non-coding RNA overexpressed in gefitinib-resistant cells, similarly recruits EZH2. Through this interaction, EZH2 suppresses the expression of the tumor suppressor gene DUSP1, thereby activating the ERK signaling pathway and consequently enhancing gefitinib resistance [86].

Studies have revealed that LINC01116 is upregulated in gefitinib-resistant NSCLC cells and tissues, where it negatively regulates the expression of Interferon Induced Protein 44 (IFI44). IFI44 is involved in the interferon (IFN)/STAT1 signaling pathway. Silencing LINC01116 increases IFI44 expression, thereby reversing gefitinib resistance in drug-resistant PC9 cells [87].

In LUAD cells, ZEB1 trans-activates lncRNA SNHG15. SNHG15 sponges the tumor suppressor miR-451, thereby relieving the inhibitory effect of miR-451 on multidrug resistance protein 1 (MDR-1), consequently enhancing resistance to gefitinib [88].

In NSCLC disease progression cases, the expression of LCETRL3 or LCETRL4 is significantly elevated. LCETRL3 stabilizes the RNA-binding protein TDP43 by inhibiting its degradation via the ubiquitin-proteasome pathway, thereby activating NOTCH1-PTEN-AKT signaling. LCETRL4 binds to the oncoprotein EIF2S1, reduces its ubiquitin-proteasome-mediated degradation, and thereby stabilizes EIF2S1. This stabilization activates the PDK1-AKT signaling axis in NSCLC, ultimately leading to a significant increase in gefitinib resistance [89].

LncRNA NEAT1_1 is upregulated in gefitinib-resistant LUAD cells. By sponging miR-338-3p, NEAT1_1 alleviates the suppression of aldo-keto reductase family 1 member C1 (AKR1C1), thereby promoting AKR1C1 expression. As a key regulator of ferroptosis, the upregulation of AKR1C1 inhibits ferroptosis, ultimately enhancing gefitinib resistance in LUAD cells [90].

LncRNA GAS5 is downregulated in lung adenocarcinoma tissues. *In vitro* and *in vivo* experiments demonstrate that combined therapy with gefitinib and lncRNA GAS5 overexpression reduces EGFR

phosphorylation and downstream signaling protein expression. Mechanistically, lncRNA GAS5 modulates gefitinib sensitivity through suppression of IGF1R [84].

CircFBXW7 is significantly downregulated in osimertinib-resistant cell lines. It encodes a short polypeptide that binds to β-catenin in an m6A modification-dependent manner, inducing β-catenin ubiquitination and degradation, thereby suppressing Wnt signaling pathway activation. Furthermore, circFBXW7 inhibits cancer stem cell self-renewal capacity and resensitizes drug-resistant lung cancer cells to osimertinib [91].

CircASK1 is significantly downregulated in gefitinib-resistant LUAD. It encodes the ASK1-272a.a protein that competitively binds to Akt1, antagonizing Akt1-mediated phosphorylation and inactivation of ASK1. This mechanism activates the ASK1/JNK/p38 signaling pathway, promotes apoptosis, and enhances cellular sensitivity to gefitinib [92].

CircRNA IGF1R synergizes with gefitinib to prevent tumor regrowth after drug withdrawal. cIGF1R interacts with RNA helicase A to suppress IGF1R mRNA splicing, thereby negatively regulating the IGF1R signaling pathway. Additionally, the C-IGF1R peptide encoded by cIGF1R restricts mitophagy and promotes the transition from drug-tolerant persister (DTP) states to apoptosis [93].

4.5. Epigenetic remodeling and ncRNA–epigenome interplay

Epigenetic remodeling plays a pivotal role in cancer progression, particularly in modulating drug resistance in lung cancer. NcRNAs act as key regulators of the epigenome by interacting with DNA methylation modifiers, histone-modifying enzymes, and chromatin-remodeling complexes. This ncRNA–epigenome interplay can silence tumor suppressor genes or activate oncogenic pathways, contributing to chemoresistance. Understanding these mechanisms offers potential therapeutic strategies, such as targeting ncRNA-epigenetic networks to reverse drug resistance in lung cancer patients.

MiR-449a reverses phosphatase and tensin homolog (PTEN) promoter methylation in gefitinib-resistant NSCLC cells, thereby increasing PTEN expression to suppress the PI3K/Akt signaling pathway and exert tumor-suppressive effects in EGFR-TKI-resistant NSCLC. Its expression is negatively regulated by Nicotinamide N-methyltransferase (NNMT), which is upregulated in resistant cells [94].

LncRNA CCAT1 is significantly upregulated in tissues and cell lines of gefitinib-resistant NSCLC patients. It promotes NSCLC cell growth by enhancing cell proliferation and cell cycle progression while reducing apoptosis. Mechanistically, CCAT1 acts as a sponge for miR-218, thereby promoting the expression of miR-218's target gene Homeobox A1 (HOXA1), which ultimately enhances gefitinib resistance [95].

LINC00969 is upregulated in acquired gefitinib-resistant lung cancer cells. On one hand, it regulates H3K27me3 levels in the NLRP3 promoter region to modulate transcriptional activity; on the other hand, it modifies the m6A levels of NLRP3. Collectively, these actions suppress NLRP3 expression through epigenetic mechanisms, thereby blocking the NLRP3/caspase-1/GSDMD-mediated canonical pyroptosis signaling pathway. This inhibition confers an anti-pyroptotic phenotype to the cells, ultimately promoting resistance to tyrosine kinase inhibitors in lung cancer [96].

The ncRNAs related to EGFR-TKIs mentioned in this chapter are summarized in Table 2. These are categorized according to different pathways in Figure 2.

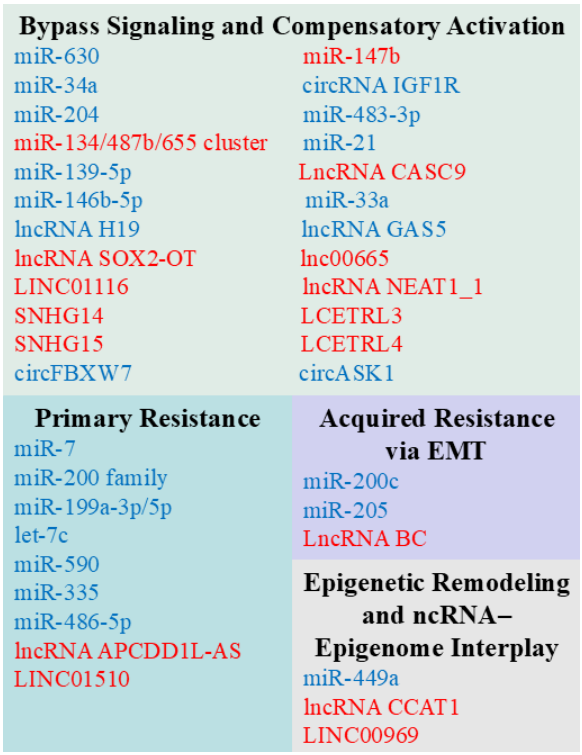

Figure 2. A summary of different EGFR-TKI resistance pathways mediated by ncRNAs.

In this concise schematic diagram, ncRNAs are categorized according to different resistance pathways. Among them, those marked in red promote resistance, while those marked in blue suppress resistance.

Table 2. The ncRNAs associated with EGFR-TKI mentioned in this review.

ncRNA	Taget	TKI	Effect on EGFR-TKI resistance	Biological effect	Reference
miR-205	ZEB1 SRC	erlotinib	reverse	Inhibition of SRC and EMT pathways	[69]
miR-33a	ABCB7 p70S6K1	gefitinib	reverse	Inhibition of ABCB7 Inhibition of p70S6K1	[76]
miR-590	EHD1	erlotinib	reverse	Inhibition of EHD1	[62]
miR-139-5p	BMP4	gefitinib	reverse	Inhibition of BMP4 Modulation of fatty acid metabolism	[77]
miR-21	TNF mRNA	erlotinib	reverse	Inhibition of TNF mRNA	[78]
miR-5693 miR-3618 miR-432-5p	unknown	erlotinib gefitinib afatinib	promote	Unknown	[97]
miR-483-3p	integrin β3	gefitinib	reverse	Inhibition of integrin β3 Inhibition of FAK/Erk pathway	[79]
miR-608	unknown	gefitinib	reverse	Unknown	[98]
miR-4513	unknown	gefitinib	promote	Unknown	[98]
miR-449a	PTEN	gefitinib	reverse	upregulation of PTEN expression Inhibition of PI3K/Akt pathway	[94]
miR-184 miR-3913-5p	unknown	osimertinib	promote	Unknown	[99]

Table 2. *Cont.*

ncRNA	Taget	TKI	Effect on EGFR-TKI resistance	Biological effect	Reference
miR-34a	MET	gefitinib	reverse	Inhibition of HGF/MET pathway	[80]
miR-7	YAP mRNA EGFRmRNA	gefitinib	reverse	Inhibition of YAP Activation of Hippo pathway Inhibition of EGFR	[57] [56]
miR-630	YAP1	gefitinib	reverse	Inhibition of YAP Inhibition of ERK	[71]
miR200 family	MIG6	erlotinib	reverse	Inhibition of MIG6	[58]
miR-200c	NOTCH1 ZEB1	gefitinib gefitiniberlotinib	reverse	Inhibition of NOTCH1 Inhibition of PI3K/AKT pathway Inhibition of ZEB1 Inhibition of EMT process and cell migration	[59] [67] [68]
miR-147b	SDHD VHL	osimertinib	promote	Inhibition of SDH complex enzyme activity Disruption of TCA cycle	[72]
miR-204	CD44	osimertinib	reverse	Inhibition of CD44 Inhibition of Lung Cancer Stemness and EMT	[73]
miR-134/487b/655 cluster	MAGI2	gefitinib	promote	Inhibition of MAGI2 Promotion of EMT	[74]
let-7c	RAS	gefitinib	reverse	Inhibition of RAS Inhibition of AKT and ERK phosphorylation	[61]
miR-335	unknown	erlotinib	reverse	Suppression of AXL-positive cell generation	[63]
miR-486-5p	Pim-1	gefitinib	reverse	Inhibition of Pim-1	[64]
miR-146b-5p	IRAK1	osimertinib	reverse	Inhibition of IRAK1 Inhibition of NF-κB activity	[75]
miR-199a-3p/5p	Rheb	gefitinib	reverse	Inhibition of mTOR pathway	[60]
lncRNA SNHG14	miR-206-3p	gefitinib	promote	Inhibition of miR-206-3p upregulation of ABCB1 expression	[81]
lncRNA H19	PKM2 GPX4	erlotinib	reverse	Inhibition of PKM2 Inhibition of AKT Phosphorylation Inhibition of GPX4 Promotion of ferroptosis	[82] [83]
lnc00665	EZH2	gefitinib	promote	Recruitment of EZH2 Activation of PI3K/AKT pathway	[85]
lncRNA CASC9	EZH2	gefitinib	promote	Recruitment of EZH2 Activation of ERK pathway	[86]
lncRNA CCAT1	miR-218	gefitinib	promote	Inhibition of miR-218 upregulation of HOXA1 expression	[95]
LINC01116	IFI44	gefitinib	promote	Inhibition of IFI44	[87]

Table 2. *Cont.*

ncRNA	Taget	TKI	Effect on EGFR-TKI resistance	Biological effect	Reference
lncRNA SNHG15	miR-451	gefitinib	promote	Inhibition of miR-451 upregulation of MDR-1 expression	[88]
LCETRL3	TDP43	gefitinib	promote	Protection of TDP43 Activation of NOTCH1-PTEN-AKT pathway	[89]
LCETRL4	EIF2S1	gefitinib	promote	protection of EIF2S1 Activation of PDK1-AKT pathway	[89]
LINC00969	NLRP3	gefitinib	promote	Inhibition of NLRP3 Repression of pyroptosis	[96]
lncRNA APCDD1L-AS1	miR-1322 miR-1972 miR-324-3p	icotinib	promote	Inhibition of miR-1322/miR-1972/miR-324-3p Inhibition of EGFR degradation	[65]
LINC01510	MET	erlotinib	promote	Enhancement of MET transcription	[66]
lncRNA BC	IMPAD1	gefitinib	promote	Enhancement of non-coding IMPAD1 transcript variant production Induction of MET	[70]
lncRNA NEAT1_1	miR-338-3p	gefitinib	promote	Inhibition of miR-338-3p Inhibition of ferroptosis	[90]
lncRNA SOX2-OT	SOX2	erlotinib	promote	Promotion of AKT/ERK Expression and AKT Phosphorylation Enhancement of SOX2 transcription	[84]
lncRNA GAS5	IGF1R	gefitinib	reverse	Inhibition of IGF1R	[84]
circPDLIM5 circPPP4R1	unknown	osimertinib	reverse	Inhibition of cell proliferation, migration, and angiogenesis	[100]
circFBXW7	β-catenin	osimertinib	reverse	Induction of β-catenin degradation Inhibition of Wnt pathway	[91]
circASK1	Akt1	gefitinib	reverse	Activation of ASK1/JNK/p38 pathway induction of apoptosis	[92]
circRNA IGF1R	IGF1R	gefitinib	reverse	Inhibition of IGF1R pathway Inhibition of mitophagy	[93]

5. Clinical implications of ncRNAs'analysis in EGFR-mutated lung cancer

By detecting and analyzing ncRNAs in patient plasma, new biomarkers can be provided for the early diagnosis, prognosis assessment, and treatment response prediction in EGFR-mutated lung cancer and drug-resistant lung cancer patients. In 2009, Seike's team conducted a comprehensive analysis of miRNA expression profiles associated with EGFR gene mutations. Through comparative analysis of miRNA expression patterns between 22 EGFR wild-type and 6 EGFR mutant cases in a cohort of non-smoking lung cancer patients, they identified 12 miRNAs that exhibited significant alterations in EGFR-mutant tumors. Notably, miR-21 demonstrated the most pronounced upregulation while miR-486

showed the strongest downregulation in EGFR-mutant lung cancer tissues compared to their wild-type counterparts. These findings reveal distinct miRNA expression signatures between EGFR-mutant and wild-type lung cancers at the molecular level, suggesting potential regulatory differences underlying these genetic subtypes [14].

In a parallel investigation, Bjaanaes' team systematically elucidated molecular differences in miRNA expression profiles between lung adenocarcinoma tissues and matched normal lung tissues through clinical cohort studies in 2014. Specifically focusing on miRNA expression disparities between EGFR-mutant and EGFR wild-type tumors, they identified 17 miRNAs with significant differential expression using microarray profiling and RT-qPCR validation, including critical regulatory factors such as hsa-miR-184, hsa-miR-339-3p, hsa-miR-148a*, hsa-miR-224*, and hsa-miR-452. The study revealed that EGFR-mutant tumors exhibit distinct miRNA expression signatures, with these differential expression patterns demonstrating significant correlation with aberrant activation of the EGFR signaling pathway. Experimental evidence confirmed that specific miRNA molecules could serve as characteristic biomarkers for EGFR mutations in lung cancer [101].

In a complementary clinical study, Szpechcinski *et al.* analyzed 66 NSCLC patient samples to explore associations between EGFR mutations and plasma circulating miRNAs. Building on prior research, they identified miR-504 as the most significant candidate among five tested miRNAs. miR-504 expression exhibited a strong correlation with EGFRactivating mutations, suggesting its potential as a non-invasive biomarker to distinguish EGFR-mutant from EGFR wild-type NSCLC. Notably, miR-504 demonstrated enhanced diagnostic utility for the EGFRexon 19 deletion subtype, a common oncogenic variant [102].

Cho *et al.* first reported that hsa-miR-145 may serve as a potential therapeutic target for EGFR-mutant lung adenocarcinoma. They discovered that the expression level of hsa-miR-145 is significantly reduced in lung adenocarcinoma. Transfection of hsa-pre-miR-145 into EGFR-mutant lung adenocarcinoma cells and EGFR wild-type cell lines demonstrated that EGFR protein expression was downregulated more prominently in the former, accompanied by a higher apoptosis rate. This indicates that the differential apoptosis induced by hsa-pre-miR-145 transfection is closely associated with EGFR mutation status, and hsa-miR-145 plays a critical role in anti-proliferation processes in EGFR-mutant lung adenocarcinoma cells [103].

Liu *et al.* utilized bioinformatics analysis combined with qRT-PCR validation on 153 primary lung adenocarcinoma (LUAD) and 54 normal plasma samples, identifying two differentially expressed circRNAs in LUAD plasma and cells: hsa_circ_0005962 (downregulated) and hsa_circ_0086414 (upregulated). Notably, elevated plasma levels of hsa_circ_0086414 showed a significant positive correlation with EGFR mutation status. Functional *in vitro* assays demonstrated that overexpression of hsa_circ_0005962 markedly enhanced LUAD cell proliferation. These findings highlight the potential clinical utility of circRNAs as non-invasive diagnostic biomarkers for LUAD [104]

Wang *et al.* focused on the mechanisms of primary resistance to EGFR-TKIs in EGFR-mutant advanced NSCLC patients. Plasma microRNA profiling revealed that miR-21, miR-27a, and miR-218 exhibited significantly elevated expression levels. Further analysis indicated that abnormal expression of these miRNAs might correlate with primary EGFR-TKI resistance in patients harboring EGFR exon 19 deletions, suggesting their potential involvement in regulating drug-resistant phenotypes [105]. miR-4513 enhanced gefitinib resistance in PC9 and H1299 cells, whereas miR-608 exerted significant inhibitory

effects. These findings propose miR-608 and miR-4513 as independent candidate biomarkers for predicting survival in lung adenocarcinoma patients following EGFR-TKI therapy [98]. Li *et al.* identified serum exosomal miRNAs for predicting osimertinib resistance through *in vitro* experiments and clinical sample analyses. Elevated miR-184 and miR-3913-5p levels were associated with osimertinib resistance in patients with EGFR exon 21 L858R mutations, while miR-3913-5p alone served as an indicator for T790M-positive patients [99]. miR-5693, miR-3618, and miR-432-5p promoted survival of multiple lung cancer cell lines exposed to erlotinib, gefitinib, and afatinib. Notably, miR-432-5p was upregulated in NSCLC patient samples and mediated the development of erlotinib resistance in initially drug-sensitive NSCLC cells [97]. Chen *et al.* established multiple osimertinib-resistant cell lines, systematically analyzed their circRNA expression profiles, and investigated the biological roles of the most dysregulated circRNAs, circP-DLIM5 and circPPP4R1, *in vitro*. Inhibition of circP-DLIM5 and circPPP4R1 significantly promoted cell proliferation, migration, and angiogenesis. This study reveals that circRNAs may serve as promising biomarkers for osimertinib resistance in NSCLC [100].

6. Other ncRNAs

In addition to miRNAs, lncRNAs, and circRNAs, NcRNAs also include piRNAs, tRNA fragments, enhancer RNAs, and small nucleolar RNAs (snoRNAs) [106].

PIWI-interacting RNAs (piRNAs) were initially discovered in animal germline cells and play a crucial role in germline development. They function by binding to members of the PIWI protein family, participating in the regulation of transposon silencing and gene expression. The primary function of piRNAs is to protect the genome from transposon insertional mutations and to maintain genomic stability during gametogenesis [107]. Additionally, piRNAs may be involved in regulating mRNA splicing, translation, and degradation. Dysregulation of piRNA and PIWI protein expression has been observed in various types of cancer and is associated with poor prognosis, suggesting their potential use as cancer biomarkers [108,109].

tRNA-derived fragments (tRFs) are a class of emerging small non-coding RNAs generated by the cleavage of mature tRNAs or tRNA precursors. tRFs can regulate cellular viability, differentiation, and homeostasis through various mechanisms, making them key regulators in human diseases, including cancer. Moreover, there is growing evidence that extracellular tRFs can serve as promising diagnostic and prognostic biomarkers for cancer liquid biopsies [110].

snoRNAs are conserved, metabolically stable RNAs that range in length from 60 to 300 nucleotides. snoRNAs are classically localized in the nucleolus and play a critical role in RNA modification and pre-ribosomal RNA processing. Recent studies have found that many snoRNAs are dysregulated in cancer, showing differential expression across cancer types, stages, and metastasis, and they can actively alter disease progression [111].

Enhancer RNAs (eRNAs) are a class of non-coding RNAs (ncRNAs) transcribed from enhancer regions and serve as key regulatory elements in gene expression, playing a significant role in transcriptional regulation [112]. There is growing evidence that eRNAs are frequently dysregulated in cancer. Enhancer activation and eRNA transcription are also relevant in inflammatory responses [113].

Although existing studies have demonstrated that piRNAs, snoRNAs, tRNA fragments, and enhancer RNAs (eRNAs) play significant roles in the development of cancer, there are few reports on

their interactions and connections with the EGFR pathway. Therefore, further investigation into the potential links between these ncRNAs and EGFR signaling not only deepens our understanding of the pathogenesis of cancer but also provides a theoretical basis for developing novel therapeutic strategies.

7. Conclusions

This review systematically elaborates the dynamic regulatory relationship and clinical significance between ncRNA and the EGFR signaling pathway in lung cancer. Recent studies have revealed a complex bidirectional regulatory network between ncRNA and the EGFR pathway: on one hand, EGFR can affect the expression of ncRNA through transcriptional regulation and epigenetic modification; on the other hand, ncRNA feedback regulates EGFR signal activity by targeting EGFR and its downstream effector molecules. Furthermore, this review summarizes the multi-dimensional mechanisms of ncRNA-mediated EGFR-TKI resistance, including regulation of drug metabolism, epigenetic remodeling, pro-survival signal compensation activation, and maintenance of tumor stem cell characteristics.

However, there are still several critical issues in current research that need to be addressed. The mechanisms underlying the functional heterogeneity of ncRNAs remain unclear. The same ncRNA may exhibit dual functions of either promoting or inhibiting cancer in different lung cancer subtypes or microenvironments, and this contradiction needs further analysis from the perspectives of spatiotemporal specificity or cell context dependency. Meanwhile, there are limitations in clinical translational research; most ncRNA studies are confined to cellular or animal models and lack large-scale clinical cohort validation. The sensitivity and specificity of circulating ncRNAs (such as exosomal miRNAs) as resistance biomarkers need to be validated through clinical trials. Furthermore, the dynamic evolution of resistance mechanisms still requires in-depth exploration, for example, how ncRNAs participate in the transition of EGFR-TKI resistance from “drug-tolerant persistence (DTP)” to “complete resistance”, and whether tumor heterogeneity leads to regional differences in the ncRNA regulatory network. In terms of technological development, technical bottlenecks limit the depth of research. The accuracy of existing ncRNA detection technologies in quantifying low-abundance ncRNAs is limited, necessitating the development of highly sensitive methods. Additionally, the stability and targeting efficiency of delivery systems for targeting ncRNAs *in vivo* still need optimization.

In the future, mechanistic research should integrate single-cell sequencing and spatial transcriptomics to decipher the cell-type-specific functions of ncRNAs within the tumor microenvironment. Organoid models should be utilized to simulate the role of ncRNA-EGFR interactions in the evolution of drug-resistant clones. For clinical translation, a liquid biopsy panel based on combinations of ncRNA biomarkers should be designed for dynamically monitoring drug resistance, while exploring strategies that combine ncRNA with targeted therapy. In terms of technological innovation, CRISPR-based ncRNA editing tools need to be developed for precise regulation of specific ncRNA expression, and exosome carrier technology should be optimized to achieve targeted delivery of ncRNA mimics or inhibitors. Future research requires multilevel collaboration from basic science to clinical application, driving the translation of ncRNA research achievements into precision diagnosis and treatment, and providing new strategies for reversing NSCLC drug resistance.

Authors' contribution

Conceptualization, Y.S. (Ying Sun) and R.Y. (Rong Yang); investigation, Q.S. (Qin Sheng), R.S. (Ruoming Shen) and Y.Z. (YiXuan Zhao); resources, Q.S. (Qin Sheng), R.S. (Ruoming Shen) and Y.Z. (YiXuan Zhao); writing—original draft preparation, Q.S. (Qin Sheng) and R.S. (Ruoming Shen); writing—review and editing, Q.S. (Qin Sheng), R.S. (Ruoming Shen) and Y.Z. (YiXuan Zhao); visualization, Q.S. (Qin Sheng); supervision, Y.S. (Ying Sun) and R.Y. (Rong Yang); project administration, Y.S. (Ying Sun) and R.Y. (Rong Yang); All authors have read and agreed to the published version of the manuscript.

Conflicts of interests

The authors declare no conflicts of interest.

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