# Non-coding RNA and lung cancer progression

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**Abstract:** Lung cancer (LC) is a major killer disease globally. This situation is further supported by yearly increase in new LC cases and its poor 5-year survival which is less than 15%. Although a large percentage of LC cases have been attributed to smoking, a considerable amount of nonsmokers also develops this disease, thereby suggesting a genetic and/or epigenetic undertone to LC development. Several growth-related genes such as epidermal growth factor receptor (*EGFR)* and vascular endothelial growth factor (*VEGF)* as well as tumor suppressor genes such as *p53* have been implicated in LC pathogenesis and progression. Likewise, the genome only contains approximately 1% of coding regions. Hence, noncoding portion of the genome such as noncoding RNAs (ncRNAs) has been studied and discovered to play a cogent role in LC pathogenesis. More precisely, microRNAs (miRNAs) and long ncRNAs (lncRNAs) have been studied for decades. Posttranscriptional gene modulation function of miRNAs is well established and characterized. Likewise, the antagonizing interaction between lncRNAs and miRNAs had also been proven to further control gene expression during healthy and disease conditions like LC. More recently, renewed attention toward circular RNAs [circular RNAs (circRNAs)] study showed that circRNAs can also sponge miRNAs to modulate gene expressions too. Hence, miRNAs, lncRNAs, and circRNAs seem to function within a circuit to optimally determine which gene is needed to be upregulated or downregulated in biological system. Therefore, this review will discuss important ncRNAs, namely miRNA, lncRNA, and circRNA in LC progression. Paracrine effect of exosomal ncRNA will be also reviewed. In addition, the prospect of these ncRNAs in enhancing better LC treatment will be highlighted as well.

**Keywords:** Circular RNA; EGFR; Lung cancer; microRNA; Noncoding RNA

## 1. INTRODUCTION

For the past few decades, lung cancer (LC) remains consistently responsible for highest global cancer mortality.[1–3] Likewise, the number of new LC cases keeps increasing every year.[2,4] In addition, 5-year survival rate for LC is less than 15%.[5] Approximately 85% of LC cases belong to nonsmall-cell LC (NSCLC) while the remaining 15% are classified as small-cell lung carcinomas (SCLCs).[5,6] The two most common histologic subtypes of NSCLC are squamous cell carcinomas and adenocarcinomas which are mainly derived from epithelial cells lining larger airways and peripheral small airways, respectively.[7] In general, oncogenesis has been established to be driven by genetic abnormalities, either tumor suppressor or supporting genes. Meanwhile, it has been discovered that only 1% of the genome code for genes. Therefore, the remaining 99% noncoding part of the genome too have garnered attention over the decades[8,9] and have been found to play a cogent role in human wellbeing as well as pathologic conditions such as lung cancer. In this review, we will focus on the roles of different noncoding RNAs (ncRNAs) in the progression of LC. In addition, we will also highlight some notable studies targeting respective ncRNAs in the detection and treatment of LC. Finally, we will postulate on the prospect of highlighted ncRNA targeting to result in therapeutic option for LC patients in future.

## 2. MicroRNA and LC

MicroRNAs (miRNAs) are endogenously expressed ncRNAs with important biological function as a posttranscriptional gene regulator.[8,9] It is unanimously believed that miRNAs bind to their respective seeding regions within the 3′ untranslated regions of their target genes.[8] This binding downregulates the expression of such target gene. A typical miRNA is generated from a long primary RNA sequence to a 20 to 22 nucleotides mature miRNA at the RNA-induced silencing complex (RISC) complex.[10] Mature miRNA acts pleiotropically by potentially targeting multiple genes, whereas some miRNAs function in a cell- or organ-specific manner.[10] For instance, miR-224 regulates oncogenic *KRAS* and *DPYSL2* genes in gastric cancer,[11] while miR-218 modulates the expression of interleukin-6/Signal transducer and activator of transcription 3 (IL6/STAT3) signaling pathway.[12] Therefore, this confers on a miRNA the potential capability to regulate multiple biological pathways that are pathogenically disrupted during disease condition such as cancer.[10,12] In LC pathogenesis and progression, several miRNAs have been identified to serve as oncogenes, tumor suppressors, and cancer progression signatures.[13]

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## 3. MicroRNA AND MODULATION OF CANCER-RELATED GENES

Cancer-related genes can be broadly divided into two parts namely oncogenes and tumor suppressor genes. Oncogenes support tumor progression while tumor suppressor gene discourages cancer development. Cancers theoretically thrive when oncogene expression are upregulated while tumor suppressor genes are downregulated in biological system. Hence, this section highlights the effects of miRNAs on oncogenes and tumor suppressor genes in relation to LC progression. For a cell to divide uncontrollably, massive proliferation-related genes will be transcribed and subsequently translated by transcription factors (TFs). Although TFs are necessary for normal biological function, tight regulation of their production and degradation is the key to proper homeostasis. Dysregulation of TFs is a common cause of malignancy such as LC. Hence, miRNAs that target these oncogenes are known as tumor suppressor miRNA. For example, Feliciano et al used microarray to identify miR-99a as a differentially expressed miRNA targeting E2F2 (E2F TF 2) and EMR2 (EGF-like module-containing, mucin-like, hormone receptor-like 2) to repress epithelial-to-mesenchymal transition (EMT) in NSCLC.[14] MiR-661 affected EMT process and metastasis of NSCLC.[15] Similarly, miR-218 was also found to directly target Slug and ZEB2 to promote LC metastasis.[16] In addition, miR-200 family members (miR-200a, miR-200b, miR-200c, miR-429, and miR-141) have been known to play crucial roles in the suppression of EMT.[17] Another miRNA family strongly implicated in LC progression is the let-7 family miRNAs.[7] Expressions of let-7 family miRs was discovered to correlate with LC disease progression as well as clinical staging.[7]

miRNAs also interfere with the genes acting along the proliferative signaling pathways in the cell. Modulation of the expression of these signaling pathways consequently increases the activities of these proteins in order for cancer tumorigenesis and progression to be sustained. On this note, it was reported that miR-24-3p promoted cell migration and proliferation in vitro by targeting SOX7 in NSCLC[18,19] and autophagy in SCLC.[20]

miRNAs targeting tumor suppressors are always downregulated in order for cancer cells to survive. Several studies have discovered that miR-185 was significantly downregulated in NSCLC clinical samples and cell lines. Overexpression of miR-185 suppressed NSCLC cell growth, migration, and invasion in vitro, and in vivo models.[21–23] One study even showed that exosomal miR-185 level can correlate with worse clinical disease progression.[23] Likewise, depleted miR-185 in NSCLC was proved to increase drug resistance by increased drug resistance transporter gene *ABCC1*.[24] Likewise, repression of Ataxia telangiectasia and Rad3-related protein (ATR) pathway by miR-185 was found to enhance proliferation inhibition and radiation-induced apoptosis.[25] Conversely, Zhang et al reported that NSCLC progression is associated with higher miR-185 expression which is supported by hypoxia increase.[26]

Notable tumor suppressor gene *p53* had also been implicated to be affected by miRNA in LC.[27,28] The tumor suppressor p53 is central to many cellular stress responses including LC development.[29] miR-125a-5p induced apoptosis in LC cell line by increasing p53 mRNA and protein expression.[30] This study provides an insight into the roles of the miR-125a family in LC.[30] Park et al found out that miR-29 family members (miR-29a, miR-29b, and miR-29c) upregulate p53 levels to induce apoptosis in a p53-dependent manner. Furthermore, the group also showed that miR-29 family members directly suppress negative regulators of p53 known as p85α (the regulatory subunit of PI3 kinase) and CDC42 (a Rho family GTPase).[29]

## 4. MicroRNA AS BIOMARKER OF LC

Several clinical trials have attempted to discover the best miRNA-based noninvasive method of detecting LC and its progression.[7,31,32] Landi et al previously summarized many clinically trials validated miRNA biomarkers which have been found to correlate with LC progression and staging.[7] Maintenance of physiological homeostasis is governed by tight regulation of all biological molecules, and miRNAs are not an exception. Recently revived studies on other nonconventional RNA transcripts have identified and reaffirm the salient function of a group of ncRNAs called circular RNAs [circular RNAs (circRNAs)]. More importantly, these circRNAs have been shown to modulate miRNA expression and function.

## 5. CircRNA IN LC

circRNA are ncRNA transcripts formed by nonconventional alternative splicing called backsplicing.[33,34] The 3′ end of a downstream exon is covalently liked with the 5′ end of an upstream exon forming a closed RNA transcript.[35,36] Although first identified in early 1990s, circRNA was proven to be important during development, conserved along the evolutionary tree, and could be tissue and cell specific in eukaryotes in early 2000.[34,37] Since then, dysfunctional or imbalance expression of circRNAs has been proven to affect the physiological status of organism. That is, under- and/or overproduction of certain circRNAs can determine whether an organism is in a healthy or diseased state including LC development.[38]

## 6. CIRCRNA HOMEOSTASIS: BIOGENESIS AND DEGRADATION

circRNAs were backspliced from the pre-mRNA of their respective parental genes.[33,35,37,39] Conventional splicing that generates linear mRNAs is known to be facilitated by spliceosome machinery. Likewise, researchers have also investigated the mechanism involved in backsplicing. The most widely accepted school of thought is that some RNA-binding proteins (RBP) facilitate the covalent bonding between the 3′ of a downstream exon and the 5′ of the upstream exon by binding to the flanking introns of circRNA exons to align the complementary introns. These flanking introns were discovered to contain transposable elements called *Arthrobacter luteus* restriction endonuclease (ALU) repeats. For example, Conn et al proved that Quaking protein regulates circRNA formation during EMT in human mammary epithelial cell line.[40] On the same note, muscleblind/ muscleblind-like proteins have also been identified as RBP that facilitates circRNA biogenesis in drosophila and humans, respectively.[35,41] Of note, the study by Kramer et al was also among the pioneer studies to identify that other RBPs such as hnRNP and SR proteins can also facilitate backsplicing to generate circRNAs.[33] After circRNA biogenesis, and completion of circRNAs function in biological system, they need to be degraded to bring about homeostasis. Hence, studies have also pursued the biodegradation mechanism of circRNA. Recently, Liu et al discovered that irrespective of circRNA's closed structure RNase-L can mediate global circRNA degradation during viral infection (Fig. 1).[42] This study will pave the way for future studies to further investigate the circRNA degradation mechanism during disease initiation and progression such as LC. In the meantime, present evidence shows that circRNA biogenesis and degradation are tightly regulated to maintain homeostasis and proper immune defense, whereas imbalance of this homeostatic condition and strong immunity will determine healthy or diseased status of an organism.

## 7. DISRUPTED CIRCRNA HOMEOSTASIS IS IMPLICATED IN LC PROGRESSION

Importance of circRNA homeostasis in biological system has been highlighted in the previous section. The most unanimously agreed and studied biological function of circRNAs is their implicated in modulating gene expression by targeting pro and antioncogenic miRNAs to promote cancer progression,[43] metastasis,[16] and even drug resistance.[38]

## 8. CIRCRNA IMPLICATION IN MAJOR LC MOLECULAR SIGNALING PATHWAYS

Phenotypic expressions are combined results of genotypic events and molecular signaling. circRNAs have been established to modulate gene expressions indirectly through endogenous competition with miRNAs for binding to their gene targets. Meanwhile, one must note that gene modulation might not be biologically effective if it does not significantly affect molecular signaling to result in a phenotypic event. LC progression has been discovered to proceed through several molecular pathways including receptor tyrosine kinase, small GTPase (RAS), anaplastic lymphoma kinase (ALK), myc oncogenic transcription factor (MYC), phosphatydylinositol-3-kinase (PI3K), and so on.[44,45] Hence, this section discusses circRNA implications in some of the most paramount LC molecular signaling pathways. However, Yang et al previously reviewed few circRNAs implicated in some of these pathways in multiple cancer types.[46]

## 9. EGFR, MAPK/ERK1/2, AND ALK SIGNALING PATHWAYS

Epidermal growth factor receptor (EGFR) is mostly implicated in NSCLC which is the majority of LC cases because of its overexpression and distinct activation mutations in NSCLC.[47] More importantly, the presence of EGFR activation mutation is necessary for the administration of targeted therapy known as EGFR tyrosine kinase inhibitors (EGFR-TKI).[48,49] Chen et al recently showed that the global physiological circRNA expressions were disrupted in LC cell lines with EGFR activation mutation and drug resistance resulting in several circRNA upregulation and downregulation.[50] On the same note, overexpression of circRNA ciRS-7 (CDR1as) was found to increase the expression of EGFR and downstream p110 kinase promoting cell proliferation in NSCLC.[51] Likewise, hsa_circ_0012673 was reported to worsen NSCLC prognosis and increase tumor growth in xenograft model via upregulating ErbB3, a member of EGFR family, expression.[52] Circular RNA F-circEA-2a derived from *EML4-ALK* fusion gene was reported to promote cell migration and invasion in NSCLC.[53]

## 10. PI3K/AKT, MYC WNT/β-CATENIN, AND OTHER SIGNALING PATHWAYS

Protein 3-phosphoinositide-dependent protein kinase-1, a master kinase crucial to the activation of proliferative Akt signaling, was targeted by circRNA hsa_circ_0004015 through sponging of miR-1183.[54] Recently, circFGFR3 was discovered to promote NSCLC cell invasion and proliferation by competitively binding miR-22-3p to increase Akt and Erk1/2 phosphorylation (p-AKT, and p-ERK1/2) as well as Galectin-1 expression.[55] Hsa_circRNA_103809 promoted the expression of ZNF121 by sequestering miR-4302 which consequently enhanced MYC protein level to promote proliferation of LC cells.[56] cir-ITCH was proven to inhibit Wnt/β-catenin signaling in LC cells. Overexpression of cir-ITCH significantly suppressed the expression of β-catenin and inhibited cell proliferation through miR-7 and miR-214.[43] circPRKCI prevented miR-545 and miR-589 from repressing the expression of a pro-tumorigenic TF E2F7 by serving as miR-545 and miR-589 endogenous binding competitor.[57] Also, HGF/c-Met was found to regulate the expression of SAE2 and circRNA CCDC66 to subsequently increase EMT and drug resistance of lung adenocarcinoma cells.[58]

## 11. LNCRNAS AND LC

lncRNAs are classified as RNA transcripts that are longer than 200 nucleotides but cannot be translated into protein. ncRNAs, lncRNA inclusive, have been found to deliver housekeeping functions in several biological processes by taking part in the regulatory mechanism of gene expression at the transcriptional and posttranscriptional level.[59] In addition, lncRNAs have important roles in many diseases including cancer. It has been shown that abnormal expression of lncRNAs is observed in several human cancers. A number of studies have shown that many lncRNAs can function as oncogenes in cancer development through the

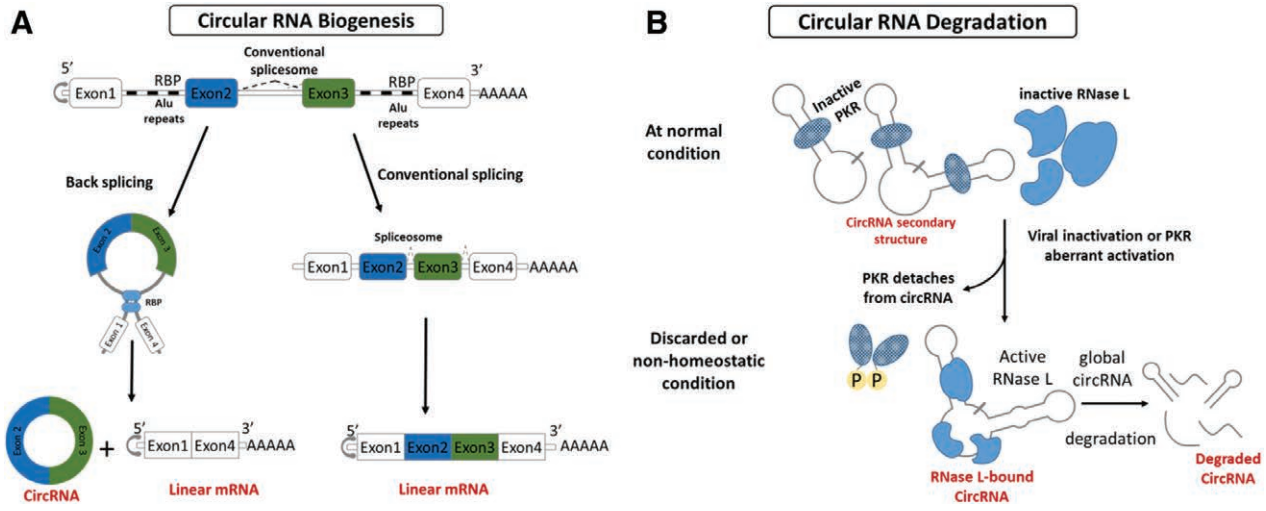


**Fig. 1** circRNA biogenesis and degradation. A, Unanimously agreed notion about circRNA biogenesis. B, Inspired by the study by Liu et al.[42] ALU repeat, ALU transposable element; circRNA, circular RNA; PKR, protein kinase R; RBP, RNA-binding protein.

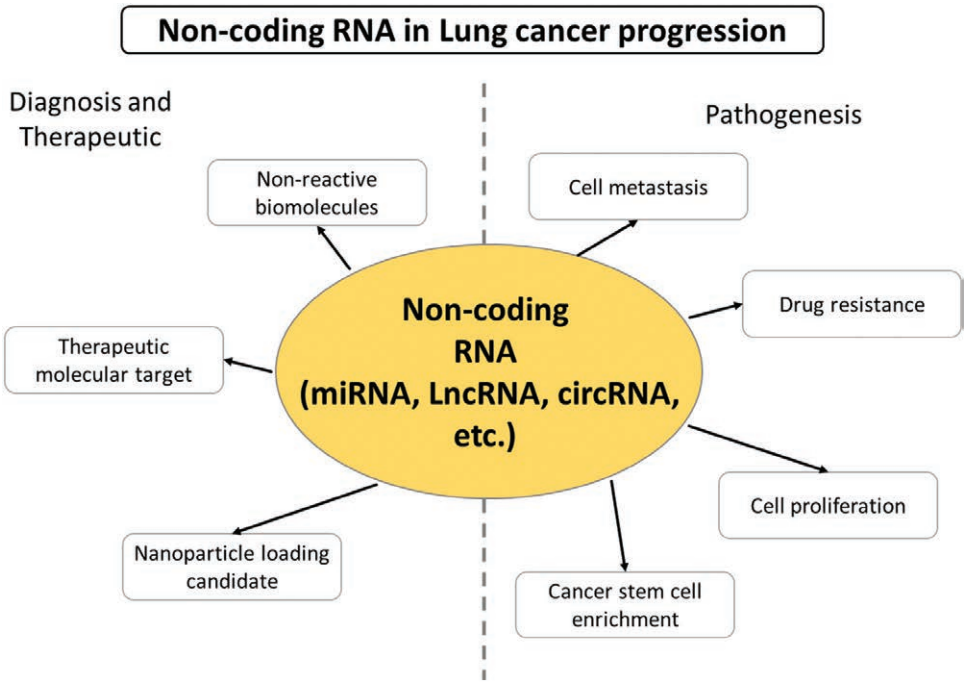


**Fig. 2** Schematic diagram of implications in LC progression, diagnosis, and treatment. circRNA, circular RNAs; LC, lung cancer; lncRNAs, long ncRNA; miRNA, microRNAs.

induction of cell cycle progression, cell proliferation, and invasion, antiapoptosis, and metastasis.[59,60] However, the biological and molecular mechanisms of lncRNA involvement in LC have not yet been fully elucidated. More so, studies have shown that oncogenic lncRNAs have the potential to become promising biomarkers and might be potent prognostic targets in cancer therapy.[61] This section summarizes studies highlighting lncRNA involvement in LC.

The expression of LINC01123 was reported to be upregulated in NSCLC and predicted to sponge miR-199a-5p. Meanwhile, miR-199a-5p was shown to modulate the expression of c-Myc transcripts in NSCLC cell line. In addition, the expression of LINC01123 upregulated the expression of c-Myc by sponging miR-199a-5p, leading to increased proliferation and aerobic glycolysis.[62] Similarly, overexpression of lncRNA KCNQ1OT1 was found to be closely associated with tumor size, lymph node metastasis, and tumour node metastasis cancer staging (TNM) stage in NSCLC. NSCLC patients with high lncRNA KCNQ1OT1 expression level have worse prognosis compared to that in low expression group.[63] On the same note, long intergenic ncRNA for kinase activation (LINK-A), lncRNAs are formed from intronic portion of lncRNAs, was also discovered to be overexpressed in metastatic NSCLC and associated with higher mortality rate and lower progression-free survival rate within 2 years of discharge.[64] Mechanistically, LINK-A may promote the migration and invasion of NSCLC by activating Akt signaling.[64] Meanwhile, c-Myc expression was upregulated by LINC01123/lncRNA MINCR which consequently upregulated downstream cyclin A, cyclin D, CD4, and CDK2, as well as apoptosis-associated Bcl-2 but downregulates PARP-1. Altogether, this led to abnormal cell cycle and inhibition of apoptosis.[65]

EMT symbolizes the advanced stage of LC characterized by metastasis. Upregulation of lncRNA HOXA-AS2 in NSCLC was observed to be remarkably associated with distant metastasis and poor prognosis of NSCLC patients. Majorly by regulating miRNA-216a-5p and EMT signaling pathway in NSCLC, lncRNA HOXA-AS2 was found to be able to promote the malignant progression.[66] PI3K/Akt/mTOR signaling pathway was also said to be implicated in upregulated lncRNA OECC-induced cell proliferation and cell metastasis in human LC.[67] Conversely, lncRNA myocardial infarction-associated transcript silencing, via parental gene knockdown, epigenetically reduced matrix metalloproteinase 9 (MMP9) transcriptional activity, whereas its overexpression was associated with LC advanced tumor stage via decreased cell proliferation, migration, invasion, and cell cycle arrested in G1 phase.[68]

On another note, Lin et al discovered that lncRNA TUG1 was significantly downregulated in NSCLC and led to poorer survival.[69] Tumor suppressor role was also ascribed to LncRNA MIR22HG, because it was discovered to inhibit multiple cell cycle-related genes in human primary lung tumors.[70] Its downregulation in LC was associated with poor patient survival.[70] Furthermore, lncRNA CASC2's significant decrease in NSCLC was also found to be involved in the development and progression of NSCLC. Lower expression of its parental gene *CASC2* significantly promotes NSCLC cell proliferation both in vitro and in vivo.[71] Likewise, lncRNA SPRY4-IT1 was reported to regulate the invasive and metastatic ability of NSCLCs partially through its regulation of the EMT. Its significant decrease in NSCLC tissues mediated by EZH2 may serve as negative prognostic factor for NSCLC patients, indicative of poor survival rates, and higher risk for cancer metastasis.[72]

## 12. EXOSOMAL ncRNAS' PARACRINE EFFECT IN LC

Exosomes are 40- to 100-nm nanosized vesicles that are released from many cell types into the extracellular space and widely distributed in various body fluids. Exosomes are released by exocytosis process when multivesicular bodies fuse with the plasma membrane.[73] There are two types of exosomes: the immunologically active exosomes involved in antigen presentation and co-stimulation and the second type that contains RNA and mediates genetic communication between cells.[74] Over the past decades, there has been a growing body of evidence showing the

important roles of exosomes as mediators of cell-to-cell communications not only in physiological processes but also in pathological conditions such as neurodegenerative diseases and cancer development and progression. Exosomes can alter the transcriptome and function of the cell with the RNA strands they carry when transferred to the recipient cell. Besides, nucleic acids (DNA, RNA), proteins, nucleoproteins, and various enzymes that exosomes carry can be utilized for signal transduction.[75] Presented below are the roles of exosomal ncRNAs in lung carcinogenesis with the main emphasis on paracrine effect exerted by these "natural nanoparticles" on LC progression.

Kim et al examined changes in exosomal cargo upon transforming growth factor-β1-induced EMT in A549 lung adenocarcinoma cells and found that the protein content of the exosomes reflects cell phenotype shifting while exosomal miR-23a enrichment was observed after mesenchymal transition.[76] Exosomes released from highly metastatic LC cells and human late stage LC serum were found to induce vimentin expression, and EMT in recipient human bronchial epithelial (HBE) cells, resulting in enhanced migration, invasion, and proliferation in noncancerous recipient cells.[77]

Exosomes derived from A549 cells upon cisplatin [Diamminedichloridoplatinum (II) (DDP)] exposure resulted in attenuated sensitivity of other A549 cells to DDP, which is probably mediated by miRNAs and mRNA exchange.[78] In addition, it was observed that exosomes confer recipient cells' resistance to DDP in an exosomal miR-100-5p-dependent manner targeting mTOR.[79] Exosomes released from gefitinib-resistant PC-9GR cells could transfer resistance to its recipient sensitive PC-9 cells which might involve intercellular exchange of exosomal miR-214.[80] Likewise, lncRNA H19 was secreted by packaging into exosomes and then can be transferred to nonresistant cells, thus inducing gefitinib resistance. This suggested exosomal H19 may be a promising therapeutic target for EGFR+ NSCLC patients.[81] LncRNA RP11-838N2.4 could be packaged into exosomes and delivered to sensitive cells, thus disseminating erlotinib resistance in NSCLC.[82]

Exosomal ncRNAs might also be involved in tumor angiogenesis induced by cytokines or growth factors. Exosomal miR-21 derived from transformed HBE cells leads to STAT3 activation, which increases vascular endothelial growth factor (VEGF) levels in recipient cells, thereby promoting angiogenesis in human umbilical vein endothelial cells (HUVECs).[83] Additionally, increased TIMP-1 led to the upregulation of miR-210 in a CD63/PI3K/AKT/HIF-1-dependent pathway in lung adenocarcinoma cells. Upon the overexpression of TIMP-1 in tumor cells, miR-210 was accumulated in exosomes, which promoted tube formation activity in HUVECs.[84]

Exosomes have emerged as a major contributor to tumor progression by transferring proteins/RNAs/DNAs and immunosuppressive molecules.[85] Exosomal miRNAs (miR-21/29a) derived from LC cell lines A549 and SK-MES bind to receptors of the Toll-like receptor (TLR) family, murine TLR7, and human TLR8, in immune cells, initiating an inflammatory response and ultimately promoting tumor growth and metastasis.[86] Cai et al found that by increasing MMP expression via Fas signaling, activated T cell exosomes can induce melanoma and LC cell metastasis, revealing a new mechanism of tumor immune escape.[87]

## 13. CONCLUSION AND FUTURE PROSPECT

Arguably, the most represented ncRNA in both biomedical research and therapeutics are still miRNAs. Although, other ncRNA such as lncRNA, and more recently circRNAs have also been found to significantly participate during LC progression. Other than the fact that many ncRNAs have been proven to be reliable noninvasive biomarker for LC, many of them have also been shown to possess functional qualities at the molecular level. Therefore, targeting such ncRNAs could expand the treatment choice for LC. Besides, their relatively small sizes make them a good choice for packaging into nanoparticles for more effective targeting of LC. More so, last year, Food and Drug Administration (FDA) approved the very first small ncRNA drug, patisiran (Onpattro, Alnylam Pharmaceuticals) for the treatment of peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis which further increased the hope of using RNA to treat diseases. In addition, last month GIVLAARI™ (givosiran) was also approved for the treatment of adults with acute hepatic porphyria (AHP), another rare inherited genetic disorder. These further increased the hope of using RNA to treat diseases including LC which cancer related mortality is currently the highest.[88] In conclusion, ncRNAs are important part of the genome in which dysregulation can initiate and promote LC development. Furthermore, detection of ncRNA dysregulation can also serve as a prognostic biomarker and targeting this ncRNA can also serve as a therapeutic strategy for diseases such as LC (Fig. 2).

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