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Review Article

Non-coding RNAs and regulation of the PI3K signaling pathway in lung cancer: Recent insights and potential clinical applications

Mehrdad Hashemi [a,b], Asal Abolghasemi Fard [a], Bita Pakshad [a], Pezhman Shafiei Asheghabadi [a,b], Amineh Hosseinkhani [a,c], Atena Sadat Hosseini [a,c], Parham Moradi [a,b], Mohammadreza Mohammadbeygi Niye [a,b], Ghazal Najafi [a,b], Mohadeseh Farahzadi [a,b], Saloomeh Khoushab [a,b], Afshin Taheriazam [a,g,*], Najma Farahani [a,**], Mahya Mohammadi [d,***], Salman Daneshi [e], Noushin Nabavi [f], Maliheh Entezari [a,b,****]

[a] Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[b] Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[c] Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[d] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Department of Public Health, School of Health, Jiroft University of Medical Sciences, Jiroft, Iran
[f] Independent Researcher, Victoria, British Columbia, V8V 1P7, Canada
[g] Department of Orthopedics, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

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ABSTRACT

Lung cancer (LC) is one of the most common causes of cancer-related death worldwide. It has been demonstrated that the prognosis of current drug treatments is affected by a variety of factors, including late stage, tumor recurrence, inaccessibility to appropriate treatments, and, most importantly, chemotherapy resistance. Non-coding RNAs (ncRNAs) contribute to tumor development, with some acting as tumor suppressors and others as oncogenes. The phosphoinositide 3-kinase (PI3Ks)/AKT serine/threonine kinase pathway is one of the most important common targets of ncRNAs in cancer, which is widely applied to modulate the cell cycle and a variety of biological processes, including cell growth, mobility survival, metabolic activity, and protein production. Discovering the biology of ncRNA-PI3K/AKT signaling may lead to advances in cancer diagnosis and treatment. As a result, we investigated the expression and role of PI3K/AKT-related ncRNAs in clinical characteristics of lung cancer, as well as their functions as potential biomarkers in lung cancer diagnosis, prognosis, and treatment.

1. Introduction

Lung cancer (LC) is the most lethal kind of cancer, affecting 11.6 % of all malignancies [1,2]. LC is classified into two types: small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). NSCLC is responsible for 80–85 % of all LC patients and has three subtypes: large cell carcinoma (LCC), squamous cell carcinoma (SCC), and adenocarcinoma (ADC) [3,4]. SCC typically develops in the primary bronchial tubes, whereas ADC develops in the peripheral bronchus and pulmonary tissues, eventually spreading to extrathoracic tissues. According to recent research, all subtypes of lung cancer have heterogeneous histological and molecular characteristics [5].

Non-coding RNAs (ncRNAs) are RNAs that are transcripted but not translated into proteins [6,7]. ncRNAs are classified as either housekeeping or regulatory ncRNAs based on their cellular roles [8,9]. Housekeeping ncRNAs, such as ribosomal RNA, are required for

* Corresponding authors. Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
** Corresponding author.
*** Corresponding authors.
**** Corresponding author. Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
E-mail addresses: a.taheriazam@iautmu.ac.ir (A. Taheriazam), najmafarahani@gmail.com (N. Farahani), Mahya_mohammadi@sbmu.ac.ir (M. Mohammadi), mentezari@iautmu.ac.ir (M. Entezari).

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fundamental eukaryotic cell activity, while regulatory ncRNAs, such as MicroRNA (miRNA) [10], long non-coding RNA (lncRNA) [11], circular RNA (circRNA) [12], small interfering RNA [13], and PIWI-interacting RNA [14], are involved in a variety of cellular functions, such as DNA synthesis, proliferation, and differentiation, by modifying relevant gene transcription [6,15,16]. As a result, ncRNA dysregulation is linked to several diseases, including cancer [15,17–23]. NcRNA dysregulation has been linked to nearly all LC progression processes, including apoptotic cell death, cell division, metastasis, autophagic cell death, and cell stemness [24–27]. However, research into LC-related ncRNAs is still limited.

Growing evidence suggests that the ncRNAs-PI3K/AKT interaction is important in the molecular mechanism of lung cancer [28]. Under normal circumstances, insulin growth factors and cytokines can activate the PI3K/AKT pathway, which contributes to the control of several intracellular signaling and cellular functions, including cell growth, differentiation, and invasion, gene transcription, metabolic function, autophagy, apoptosis, infiltration, angiogenesis, and cytoskeletal reconstruction [29,30]. The PI3K/AKT pathway is abnormally activated in multiple tumors such as ovarian, lung, gastrointestinal tract, breast, liver, and osteosarcoma [31]. As a result, further research into the PI3K/AKT pathway function in tumorigenesis is essential [32]. The connection between ncRNAs and the PI3K/AKT pathway is now known to be strongly linked to numerous lung cancer characteristics, providing novel insights into lung cancer diagnosis, prognosis, and treatment [33]. In this review, we examine the biological processes and applications of the ncRNAs/PI3K/AKT pathway in lung cancer development and advancement, as well as their potential as diagnostic, prognostic, and therapeutic biomarkers in lung cancer patients.

2. An overview of the PI3K/AKT and mechanism

PI3K is a lipid kinase that functions as a receptor tyrosine kinase (RTK) and G protein-coupled receptor (GPCR) downstream agent

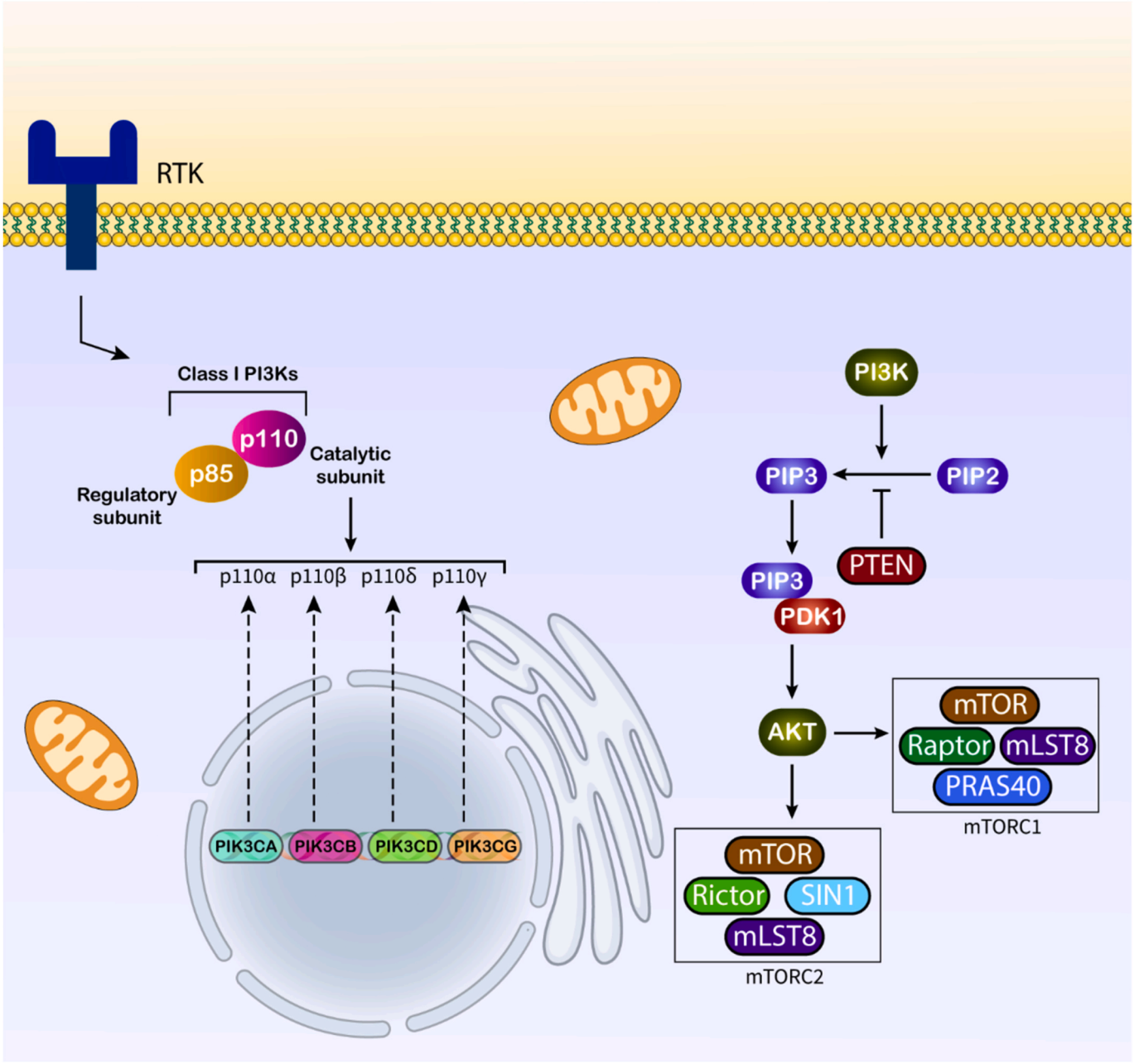

Fig. 1. A schema of the PI3K/AKT/mTOR signaling pathway.

(Fig. 1) [32,34]. According to structural and functional differences, PI3K has been divided into three classes (I, II, and III). Class I PI3K is the most commonly associated with cancer and has attracted a lot of clinical research interest [35]. Class I PI3Ks are heterodimers composed of a regulatory (p85) subunit, including IA and IB, and a catalytic (p110) subunit, including p110α, p110β, p110γ, and p110δ, which are expressed by the PIK3CA, PIK3CB, PIK3CG, and PIK3CD genes, respectively [36]. The interaction of PI3K subunits not only maintains the framework but also presents downstream regions for PI3K directly activation by RTKs and GPCRs, oncogenes like Ras via various components such as insulin, epithelial growth factor (EGF), glucose, fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) [37,38]. Class II PI3Ks are monomers with three catalytic elements (C2, C2, and C2) but no regulatory subunits [31]. They are currently critical signaling molecules that play essential functions in both biological and pathological conditions [39]. Notably, class II PI3Ks are involved in the distinct production of lipid structures, which is essential for biological functions [40,41]. Class III PI3K is composed of a catalytic (including VPS34) and a regulatory subunit, and it has been demonstrated that after activation, VPS34 regulates various protein kinases without using direct targeting signaling pathways through modulating a baseline level of mTOR complex 1 (mTORC1) and the glycogen synthetase kinase 3 (GSK3) cascade in AKT inhibitor-treated cancer patients [42,43]. These results indicate that VPS34-targeting approaches could be a promising therapeutic strategy. Fig. 2 illustrates the various isoforms of the PI3K/AKT/mTOR signaling pathway.

AKT (also referred to as protein kinase B (PKB)) is a serine-threonine kinase enzyme encoded by the PKB gene. AKT can activate the subsequent PI3K/AKT pathway by phosphorylating multiple isoforms, including AKT1, AKT2, and AKT3, which is a critical factor of the PI3K/AKT pathway [44]. When PI3K is activated, it can induce the conversion of phosphatidylinositol 3,4-bisphosphate (PIP2) to 3,4,5-trisphosphate (PIP3), and then PIP3 can bind to PDK1 and phosphorylate AKT [45]. Inhibition of AKT can also occur through dephosphorylation of CTMP, PP2A, and tcl1 [46], in which activated AKT translocates to the nuclear and cytoplasmic regions for activating or inhibiting downstream substrates, altering several cell-mediated signaling and metabolic processes and resulting in unusual cellular functions (Fig. 3) [47].

MTOR, a protein kinase targeted by the PI3K/AKT pathway, has two components: mTORC1 and mTORC2 [48]. While mTORC2 is composed of mTOR, Rictor, SIN1, and mLST8 subunits, mTORC1 is composed of mTOR, PRAS40, raptor, and mLST8 subunits and regulates cell growth via phosphorylation of elF-4E-binding protein 1 (4EBP1) and S6 kinase 1 (S6K1) [49]. mTOR complexes are involved in several biological and pathological mechanisms, such as metabolic processes, survival, angiogenesis, and immune response [50]. Akt, on the other hand, has been discovered to interact with mTORC2, activating it by phosphorylation of the tuberous sclerosis complex 2 (TSC2) [51]. As a result, inhibiting mTOR has attracted a lot of interest in human oncology research. Several studies have shown that blocking one signaling pathway can stimulate another. Inhibiting PI3K, for example, reactivates AKT via ERK2 [52]. Therefore, suppressing both the MEK and PI3K/AKT/mTOR pathways with a mixture of signaling-inhibiting drugs could potentially be a better way of targeting cancer cells than treatment with a single drug.

PTEN was first identified as a mutated lipophosphoprotein in a variety of malignancies, but it is currently recognized to be a tumor suppressor that contributes to the PI3K signaling pathway by inhibiting the reverse of PIP2 to PIP3 [53,54]. TPTEN mutations or impaired activity allow PI3K factors like AKT to be activated in the absence of additional carcinogenic stimulation [55]. PTEN normally regulates tumor signaling by dephosphorylating and targeting molecules such as PTEN, insulin receptor substrate 1 (IRS1), and focal adhesion kinase (FAK) [32,56]. Increased AKT activation is a significant tumor-causing approach in PTEN-deficient cancers [57].

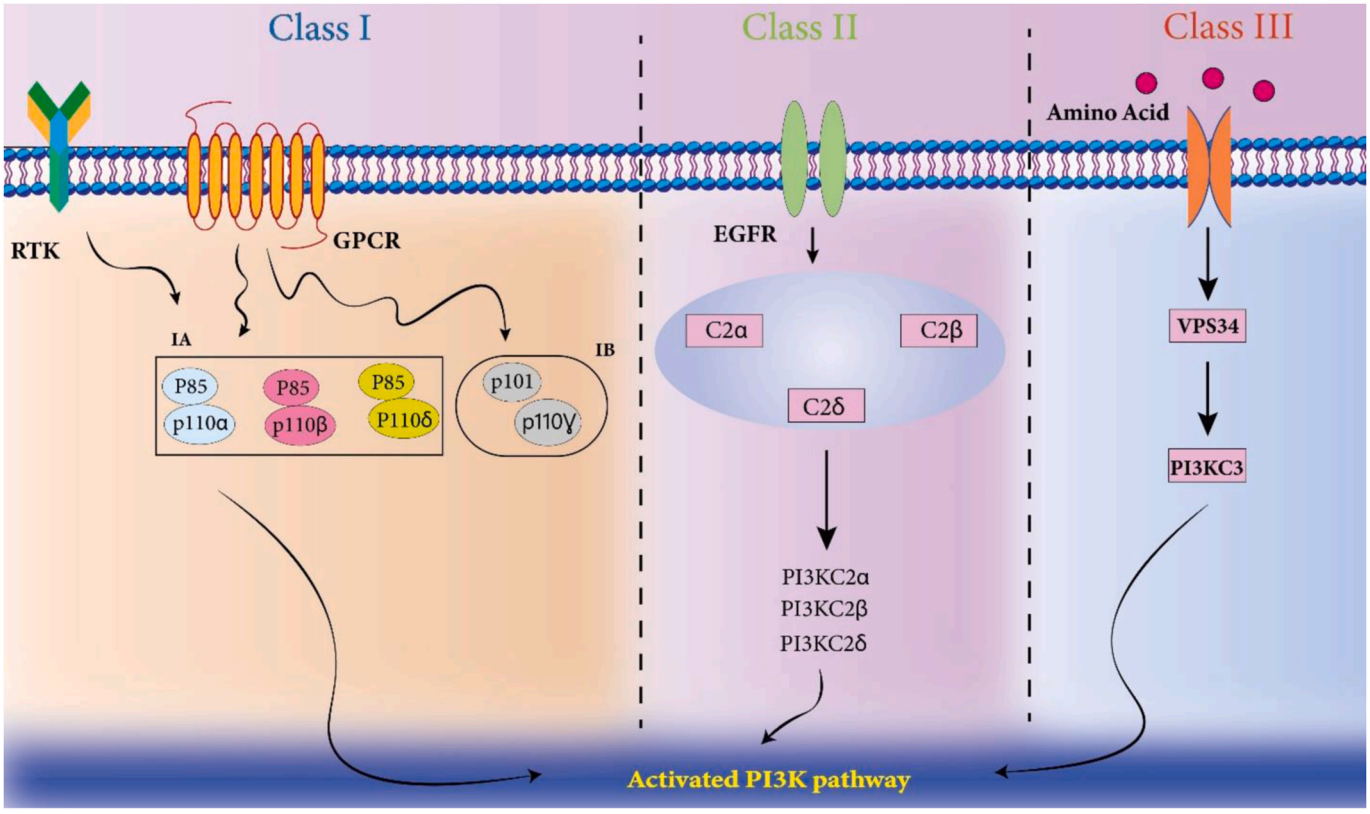

Fig. 2. Schematic view of the various isoforms of the PI3K/AKT/mTOR signaling pathway. Each isoform plays a distinct role in cellular processes, including growth, proliferation, and survival. Understanding these isoforms is crucial for elucidating their contributions to cancer biology and therapeutic targeting.

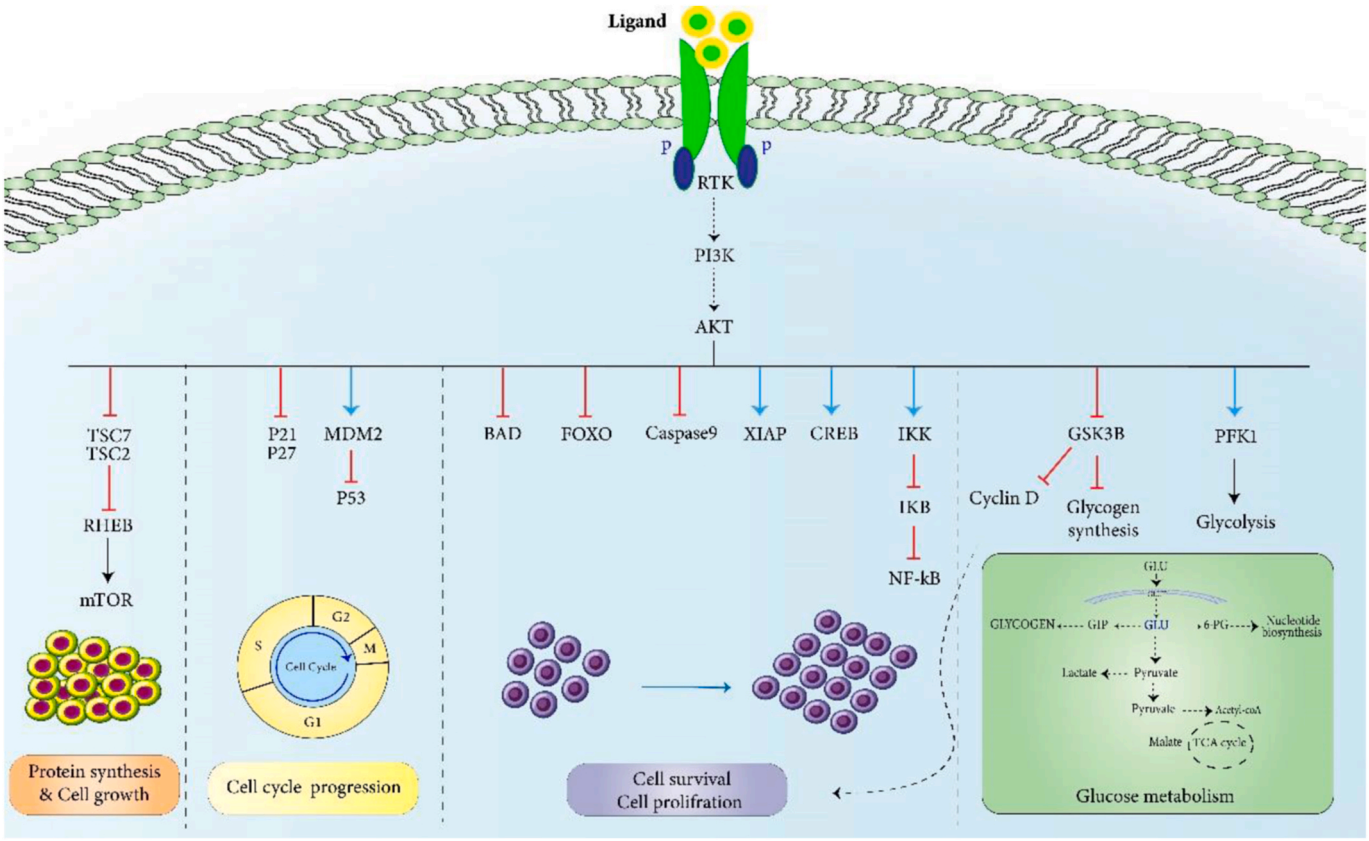

Fig. 3. This schematic illustrates the downstream pathways influenced by AKT activation. It highlights the critical signaling cascades that are modulated upon AKT activation, providing insight into their roles in cellular processes such as growth, survival, and metabolism.

3. PI3K signaling pathway and tumorigenesis

Multiple investigations have demonstrated that the PI3K/Akt/mTOR signaling pathway is related to both the onset and advancement of various cancers [58,59]. For example, PI3K/AKT mutations have been observed in nearly 70 % of breast [60] and ovarian cancers [61], with abnormal PI3K/AKT/mTOR pathway activation seen in 90 % of ADCs and 40 % of SCCs of lung cancer subtypes [62]. A variety of mechanisms, including inactivation of alterations in tumor-suppressive genes such as PTEN or INPP4B, genome-wide changes in PIK3CA, PIK3R1 (p85 regulatory member) or PIK3R2 (p85 regulatory member), and Akt members, cause this abnormal activation [63]. Furthermore, AKT is an activator of Nrf2. Nrf2 is essential for the proliferation of cancer cells through metabolic reprogramming. In the context of oncogenesis, the PI3K/AKT pathway acts as a primary proliferative signal by interacting with the NRF2 signaling pathway. It has been observed that the PI3K signaling pathway regulates NRF2 signaling independently of KEAP1 [64,65]. Cyclin-dependent kinase 20 (CDK20) functions as a regulatory factor in the cell cycle. In lung cancer cells, CDK20 competes with Nrf2 for binding to Keap1, which enhances the expression of Nrf2 and decreases ROS levels [66]. This interaction consequently supports the sustained proliferation of tumor cells. Persistent PI3K/AKT/mTOR pathway activation enhances Nrf2 activity, resulting in cellular metabolic reprogramming and promoting the excessive growth of A549 cells. The interplay between Nrf2 and the PI3K/AKT/mTOR signaling pathway contributes to the development of lung cancer. Furthermore, the increased expression of Nrf2 contributes to lung cancer advancement and increases the tumor cell's ability to escape from apoptosis [67]. During lung cancer development, Nrf2 initially acts as a tumor suppressor in early tumor stages but changes to a tumor promoter as the disease advances. Subsequently, following lung cancer development, transformation of benign adenomas into malignant ones is accelerated by the Kras/Nrf2/GPX2 and MRP4 pathways [68,69].

Several tumor mutations with distinct functions have been discovered, including gain of function (GOF) in growth factor receptor (EGFR), human growth factor receptor 2 (HER2), and mTOR, as well as loss of function (LOF) in TSC1 and TSC2 [70,71]. For instance, AKT2 overexpression has been linked to pancreas cancer, whereas AKT3 has been linked to prostate and breast cancer [72]. The PI3K pathway is disrupted by various processes, including loss of function (LOF) in PTEN and gain of function (GOF) in PI3K, TKR, or other oncogenic PI3K upstream [73–75].

3.1. Loss of function in PTEN

LOF in PTEN is found in both genetic and sporadic cancers such as brain, breast, and prostate cancer [76,77]. In addition, minor modifications in PTEN levels have been shown to affect regular cellular activity such as cancer cell migration and extracellular matrix remodeling [78]. In mice, knocking in two PTEN mutations, PTENC124S and PTENG129E, prevents PTEN lipophosphoprotein activity in the most destructive way, resulting in elevated PI3K signaling function, AKT overexpression, and tumor development [79].

3.2. Gain of function in PI3K

PIK3CA mutations or increased expression are found in three domains (including E545K, E542K, and C2) in the majority of tumors, including breast, gastrointestinal, cervical, prostate, and lung cancers [80,81]. E545K (exon 9) inhibits p110 repression by the p85 regulatory member, whereas H1047 (exon 20) increases p110 interaction with plasma membranes close to the tail of the catalytic site [82,83]. Exon 9 is more important than exon 20 in colorectal cancer, whereas exon 20 is essential in endometrial cancer, implying that different PIK3CA mutants

may have opposing effects on subsequent cancer-associated signaling [82,84,85]. Such PI3K pathway deregulation facilitates cell progression and invasion, glucose uptake and degradation, cytoskeletal reorganization, and metastasis, all of which contribute to cancer development and advancement [86,87].

On the other hand, other mutant catalytic subunits, such as p110β, p110γ, and p110δ, are uncommon, and their upregulation induces a malignant morphology in vitro [88,89]. Subunit p110β promotes cancer cell development, migration, and invasion [90]. The exact process of p110β activation in tumor cells remains unknown, but it is most likely mediated by GPCRs [91]. E633K, a p110β helical domain mutation, was discovered in a patient with breast cancer, which activates p100β by promoting its interaction with the lipid membrane [92]. It has been proposed that p110β is accountable for PIP3 restoration and AKT reactivation in HER2-positive breast cancer patients who received a p110α inhibitor, resulting in improved therapeutic activity in PIK3CA mutation breast cancers. Because of its importance in the development and activation of B and T lymphocytes, PI3Kδ is most frequently found in hematopoietic stem cells and stimulated by cytokine receptors, antigen receptors, growth factor receptors, and costimulatory receptors [93,94]. Blocking PI3Kδ causes DNA instability in B cells via activation-induced cytidine deaminase (AID) [95].

GOF mutations in PI3Kδ affect the immune system by causing a variety of deficits in B and T cell development and function. LOF mutations cause severe B cell lymphopenia and agammaglobulinemia [96]. PI3Kδ is required for AKT activation and cell growth in acute myeloid leukemia (AML) [97]. Furthermore, the p110δ protein has been discovered in melanocyte cells and may regulate breast cancer cell invasion and migration [98]. PI3Kγ accumulates in myeloid cells and modulates innate immune responses such as chemotaxis and the generation of reactive oxygen species in neutrophils in both inflammatory and malignant responses, promoting angiogenesis by upregulating VEGFα [99].

4. Role of PI3K in lung cancer

The PI3K pathway is often deregulated in lung cancer in response to genomic modifications, activating the PIK3CA gene, which encodes the p110a catalytic part, and mutated types of the Ras oncogene that influence PI3K upstream elements, leading to increased PI3K activation [100]. Mutations in two major sites of the PIK3CA gene, exons 9 and 20, are uncommon in lung cancer, occurring in approximately 5 % of NSCLC cell lines [101] and 23 % of SCLC cell lines [102]. Lung adenocarcinomas were developed in lung-specific p110a mutant mice with exon 20 mutations [103], which could be associated with resistance to RTK-targeting factors. PIK3CA genetic amplification has also been discovered in many primary NSCLC lesions [104]. Yamamoto et al. discovered PIK3CA replication, which was associated with Akt overexpression, in 33.1 % of SCC and 6.2 % of ADC, but no PIK3CA mutations were detected in SCLC cell lines [105]. Another study found that more than half of SCLC tumors and cell lines had increased PIK3CA gene replication rates [106].

AKT1, AKT2, and AKT3 gene mutations have been found in a few NSCLC tumors with AKT2 gene mutations that cause cancer development, indicating that the post-transcriptional pathway is dysregulated [107]. Excessive Akt activation has been found in primary NSCLC cell lines and has been linked to resistance to both radiation and chemotherapy, implying that it is an unfavorable predictor for patients with primary NSCLC [108]. AKT1 gene mutations were found in over 50 % of SCLC tumors, indicating that the PI3K pathway contributes to lung cancer progression [2].

PTEN deletions and missense mutations have been shown to activate the PI3K pathway in many cancers, but not in NSCLC [109]. In contrast, lung cancer frequently has a total or partial PTEN deficiency [108]. In addition, mTOR mutations have been linked to cancer cell invasion and metastasis in NSCLC models with KRAS mutations [110]. Abbasian et al. discovered that patients with early-stage NSCLC who overexpressed mTOR had a better prognosis [111].

Somatic EGFR mutations revealed that EGFR activated the PI3K pathway in lung cancers [112]. RTK inhibitors have been shown to effectively inhibit PI3K activation and induce apoptosis. In contrast, EGFR-mutant NSCLC cells showed increased PI3K activation in response to gefitinib, a tyrosine kinase inhibitor [113]. As a result, targeting the PI3K pathway in lung cancer patients with EGFR mutations who are resistant to TKIs has been proposed as a potential strategy.

Ras oncogene mutations are also common in malignancies, including lung cancer [114]. Ras GTPase binds directly to the p110a component, activating the PI3K pathway. In mice, K-Ras-mediated ADC cells were repressed by a mutation in the p110a domain that was unable to bind to Ras [115]. Furthermore, Engelman et al. demonstrated that deleting Pikr1 and Pikr2 prevents lung cancer development induced by K-Ras [116]. Even though the PI3K pathway appears to be important in K-Ras-mediated tumorigenesis, experimental findings indicate that suppressing PI3K signaling alone is unlikely to be completely efficient in stopping tumors with K-Ras mutations [117].

The PI3K/Akt/mTOR pathway is involved in LC cell development and progression through various processes, including cellular proliferative, invasive, metastatic, angiogenic, chemoresistant phenotype, metabolic rate, genetic stability, and stem cell regeneration [118]. Therefore, modifications in each part of this pathway could boost tumor dissemination and contribute to lung cancer advancement [119].

According to extensive research, targeting specific elements (such as PI3K inhibitors, AKT inhibitors, and mTOR inhibitors) can disrupt the signaling cascade, resulting in decreased tumor growth and enhanced apoptosis [120–122]. Given the significance of PI3K/Akt signaling in tumor growth, numerous PI3K inhibitors have been studied for the treatment of a variety of cancers; certain medications are currently FDA-approved for tumor treatment and cancer therapy enhancement [123]. Pan-PI3K inhibitors such as Pictilisib (GDC-0941), buparlisib (BKM120), and pilaralisib (XL147) are excellent examples of inhibitors that target p110 subunits of class IA PI3Ks. These inhibitors are more successful in treating cancer and have fewer toxicity than other PI3K inhibitors [124]. A further class I inhibitor, XL147, exhibits a high selectivity for four PI3K subtypes. In many types of tumor cell lines, XL147 reduced the production of PIP3 in the cell membrane as well as the phosphorylation of kinases like Akt, impacting genetic changes in the PI3K pathway [125]. Because there are three Akt subunits, the majority of present Akt inhibitors are pan-Akt inhibitors, and the discovery of selective inhibitors targeting the three Akt subunits will be difficult. Clinical trials are presently ongoing for several Akt inhibitors, including MK-2206, GSK-2141795, GSK-2110183, AZD5363, and GDC0068. Additionally, the combination of PI3K pathway inhibitors with other therapeutic approaches, such as chemotherapy and immunotherapy, enhances efficacy and mitigates drug resistance [126,127].

Research has shown that PTEN loss and PIK3CA mutations are significant factors in lung cancers' resistance to anti-EGFR treatments [128]. It has been shown that PTEN loss makes EGFR-mutant lung cancer patients resistant to erlotinib, an anti-EGFR drug [129]. A study on the gefitinib-resistant PC-9 lung cancer cell line found that PTEN loss was linked to increased Akt phosphorylation, which in turn activated NF-κB and changed the expression of Akt1, causing NSCLC cells to become resistant to chemotherapy drugs [130]. PTEN deficiency has been associated with elevated expression of CXCR4/CXCL12 and CXCR1/CXCL8, two proteins implicated in cancer metastasis [131]. Studies have illustrated the function of the PTEN/PI3K pathway in the development of lung cancer metastasis. In mice with lung cancer, it has been demonstrated that wortmannin, a particular Akt inhibitor, significantly lowers HIF-1α and CD34 expression as well as prevents cell migration and metastasis [132]. Similarly, it was demonstrated that Akt activity increased following RBP2 up-regulation in NSCLC cell lines [133]. According to a study, VEGF expression was lowered in A549 lung ADCs that were treated with specific siRNAs to prevent the PI3K/Akt/mTOR axis, which in turn resulted in lowered angiogenesis

[134]. Recent findings have shown that the induction of angiogenesis can be explained by the upregulation of HIF-1α and VEGF expression caused by enhanced Akt activation [135].

5. Non-coding RNAs: characteristics and potential functions

NcRNAs, including circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs), play a vital role in the regulation of various cellular mechanisms, such as cell division, proliferation, infiltration, and regeneration in various immunopathologies, including cancer [136–138].

5.1. MiRNA

MiRNAs are single-stranded, short ncRNAs with 19–25 nucleotides [139]. There are about 2300 human miRNAs, and they have the potential to post-transcriptionally modify over 60 % of the genes that encode proteins [140,141]. MiRNAs are endogenous RNA interference (RNAi) structures that originate in the nucleus (pri-miRNA), undergo assembly, and are transported to the cytoplasm as pre-miRNAs. These pre-miRNAs are subsequently converted into double-strand miRNAs, which are transported to the Argonaut complex either singly or concurrently, forming the RNA-induced silencing complex (RISC). The miRNA-guided RISC interacts with target mRNAs and regulates the expression of several genes engaged in different cellular processes via mRNA destabilization or translational inhibition [142,143]. In fact, miRNAs form a complex with miRNA-induced silencing proteins, such as GW182 and Argonaute, which inhibit the expression of specific genes by binding to slightly complementary mRNA targets [144]. Additionally, it has been found that nuclear miRNAs control the activation or suppression of transcriptional genes [145]. As well, miRNAs are promising biomarkers for diagnosing and treating disorders, including cancer.

5.2. LncRNA

LncRNAs are RNA molecules with more than 200 nucleotides that cannot code for proteins. LncRNAs are classified based on their chromosomal position, subcellular localization, or the existence of certain features [146,147]. These RNAs are categorized as sense, antisense, bidirectional, intronic, or intergenic considering their chromosomal position [148]. The protein-coding gene's AS RNA strand produces antisense (AS) lncRNAs, whereas sense lncRNAs relate to exons or introns of diverse genes that encode protein in the sense RNA position. Bidirectional lncRNA transcription happens in the reverse direction through non-coding gene promoters; intronic lncRNA transcription originates solely from introns; and intergenic lncRNA transcription occurs among two protein-coding genes [149,150]. In addition, the site of lncRNAs determines whether they are nuclear or cytoplasmic, which affects their roles. Nuclear lncRNAs control gene expression by transcription or chromosomal remodeling, while cytoplasmic lncRNAs regulate mRNA processing, stability, and protein level [151]. LncRNAs constitute the majority of ncRNAs (82 %), but they are less common, stable, and conserved than mRNA [152,153]. LncRNAs are crucial regulators involved in nearly all stages of gene expression [154,155]. Their main functional mechanism involves attaching to miRNA and post-transcriptionally inhibiting the expression of the target gene. Additionally, lncRNAs can alter gene expression by causing transcription factors (TFs) to migrate beyond chromatin [156]. Furthermore, studies have shown that lncRNAs can modify gene expression by directing the ribonucleoprotein complex to subsequence promoters of the target genes [157]. lncRNAs can also alter the synthesis, splicing, and stability of mRNA, which alters the gene transcription [155].

5.3. CircRNA

CircRNAs are covalently closed-ring single-stranded ncRNAs that are produced during the back-splicing of pre-mRNA [158]. These unique RNAs are single-stranded ncRNAs with a covalent circular structure and without 5′-cap or 3′-polyA end domains [159]. CircRNAs are mostly produced through back splicing of pre-mRNAs, with a downstream 5′-donor splice site connected to an upstream 3′-acceptor splice site [160]. Over 80 % of circRNAs are generated in the cytoplasm, primarily from exons of protein-coding genes, whereas solo gene regions may yield circulation structures [160,161]. CircRNAs are characterized according to their synthesis from various DNA sequences. Exonic circRNAs (ecircRNAs) are located in the cytoplasm and are created through alternative splicing of many exons. ecircRNAs are created by directly connecting base pairs of surrounding introns using reverse complementary Alu patterns, lariat synthesis of surrounding introns, which promotes back splicing and exon circularization, or the interacting of RNA binding proteins (RBPs)/splicing components to certain transcripts in flanking introns. Intronic circRNAs are composed of 7 nt GU-rich elements at the 5′-splice site and an 11 nt C-rich sequence at the branching site, which is sensitive to debranching enzymes [162–164]. CircRNAs can be stabilized in a variety of subcellular contexts under their closed-loop framework, which protects them from destruction by exonucleases [156]. CircRNAs play a pivotal role in regulating multiple biological events, such as chemoresistance, immunological response, gene expression, protein synthesis, and oncogenesis [138,165–167]. CircRNAs have been extensively studied for their potential to act as sponges for miRNAs, thereby attenuating the effects of the targeted mRNAs and changing associated gene activity. Furthermore, it has been demonstrated that some endogenous circRNAs with free frame reading translate into proteins [168]. Nevertheless, their possible roles remain unknown.

5.4. Other ncRNAs

Small interfering RNA (siRNA) is a type of RNA with 20–24 bp, phosphorylated 5′ and hydroxylated 3′ ends, and two overhanging bases. They function identically to miRNA in the RNAi pathway. Unlike miRNA, they are completely complementary to the targeted mRNA [169]. siRNAs are synthesized in the nuclear genome from long dsRNA, but they can also be transfected into cells. Similar to miRNA, siRNA molecules attach to RNPs in the Argonaut proteins to form RISC. When the double siRNA enters the RISC complex, it is unwrapped and converted into single-stranded siRNA [170]. Similar to miRNA, siRNA's primary function is to silence gene expression by inactivating mRNA and repressing translation. While miRNAs are more extensively employed as biomarkers in cancer diagnosis, siRNAs show promise as treatment options [171].

PIWI-interacting RNAs (PiRNAs) are 26–31 nts long and link with PIWI proteins from the Argonaute protein complex [172,173]. PiRNAs' major role in germline cells is to silence transposable elements (TE) both during and after transcription. Transcriptional silencing (TGS) induces in the nuclear genome, where the piwi-piRNA complex detects the embryonic TE transcript through complementarity before initiating suppression via interaction with the heterochromatin silenced complex. However, several genetic pathways underlying this procedure remain obscure and require further investigation. Furthermore, piwi-guided transcriptional repression alters the methylation of promoter DNA in mammals' germlines [174]. The piRNA-PIWI compound has the ability to trigger or inhibit translation during initial murine spermatogenesis, as well as alter mRNA breakdown in a microRNA-like manner afterwards [175,176]. Furthermore, piRNA activity in somatic cells is thought to be primitive and absent in certain species [177].

Short nuclear RNA (SnRNA), also known as spliceosomal RNA, is a class of single-stranded ncRNAs that have a typical length of 150 nt. SnRNAs are primarily accountable for the proper placement of the spliceosome on target pre-mRNAs [178]. SnRNA records are distinct from mRNA molecules in that the transcript cannot be cleaved and the 3′-ends are never phosphorylated, possibly to block translation. The

mature snRNA-snRNP complex is liberated from the pre-RNA component and begins its function in spliceosomes. SnRNAs are important in the regulation of cell division during human growth and development [179].

Small nucleolar RNAs (SnoRNAs) are short ncRNAs that range in length from 60 to 300 bp. The majority are found in intronic or other non-coding sections of genes that encode proteins associated with ribosome production. The snoRNA is processed in the nucleus and then in the cytoplasm before being incorporated into the snorP protein complex [180]. This procedure enhances their stability, allowing them to be integrated into the nucleus, typically in cajal bodies, which serve as the primary sites for splicing and ultimate alteration. The ultimate snoRNA synthesis is also closely related to host-gene expression. Although snoRNAs have a variety of cell functions and processes, they are not well understood. The understanding of the exact activities of these orphan snoRNAs will add to the current understanding of snoRNA pathways in both healthy and cancerous cells [181].

6. NcRNAs and regulation of the PI3K pathway in cancer

Recently, studies have been conducted on the relationship between ncRNAs and PI3K signaling in cancer. For instance, patients with NSCLC have high expression levels of the lncRNA CRNDE, which stimulates PI3K signaling to boost cell growth [182,183]. A few ncRNAs have also been shown to suppress PI3K pathway activity. Compared to normal cells, tumor cells express less of the GAS5 gene, and overexpression of lncRNA GAS5 suppresses cancer cell progression and invasion, but these inhibitory properties were decreased by PI3K-induced treatment [184–187].

One of the most significant causes of tumorigenesis is activation of the PI3K/Akt/mTOR pathway. MiRNAs are one of the most well-known regulators of this pathway through targeting the related components, including PI3K, Akt, and PTEN. MiRNAs can attach to certain mRNAs and inhibit or expedite their degradation. The PI3K/Akt pathway can also induce regulation of particular miRNA expression levels, resulting in feedback loops. Activated Akt, for example, might increase the expression of specific miRNAs, which can then influence other pathways [188–191]. CircRNAs can act as miRNA sponges, targeting mRNAs associated with the PI3K/Akt pathway. Circular RNAs sequester miRNAs, preventing them from inhibiting their target genes and so increasing gene expression. Some circRNAs can bind to and control the activity of PI3K/Akt proteins [34]. This has the ability to change the pathway's signaling patterns and downstream consequences. CircRNAs can bind to transcription factors or chromatin-modifying structures, influencing the expression of genes engaged in the PI3K/Akt pathway and potentially raising or lowering their activity depending on the surroundings. PI3K/Akt pathway activation may result in the overexpression of specific circRNAs, forming feedback cycles that influence the pathway's function [192,193]. This can either help preserve cell equilibrium or cause pathological disorders. CircRNAs have the ability to affect the location of signaling compounds within cells. CircRNAs can influence protein accessibility and functionality across the PI3K/Akt pathway by sequestering them in certain cellular regions. LncRNAs can function as "miRNA sponges," capturing certain miRNAs that would otherwise target PI3K/Akt pathway modules' mRNAs. LncRNAs attach to these miRNAs, preventing them from exerting their regulatory actions, resulting in enhanced expression of target genes [194–196]. LncRNAs can regulate gene expression in the PI3K/Akt pathway by binding to transcription factors or chromatin-modifying proteins [197,198]. This may cause alterations in the expression levels of essential pathway parts. Some lncRNAs can alter the location of signaling proteins, affecting their accessibility and function inside the cell. LncRNAs can affect the PI3K/Akt pathway's signaling consequences by sequestering proteins in the nucleus or cytoplasm [199].

We will provide an overview of the relationship between PI3K signaling in cancers and both increased and decreased ncRNAs in the following section.

6.1. PI3K/AKT signaling pathway related miRNAs in cancer: down and up-regulating role

Patients with bladder cancer have down-regulated miR-328-3p, which is linked to a lower survival rate. The mechanism by which upregulated miR-328-3p binds to the 3′ untranslated region (UTR) of ITGA5 suppresses EMT and deactivates PI3K/AKT signaling, thereby inhibiting the potential of bladder cancer cells to proliferate, migrate, and invade [200]. Further research revealed that bladder cancer patients had an unfavorable prognosis, larger tumors, an increased risk of local or distant metastases, and down-regulated miR-125b-5p. Practical analysis indicates that miR-125b-5p inhibits the PI3K/AKT pathway, which causes apoptosis and reduces bladder cancer cell migration and viability [201]. MiR-331-3p has been shown to be under-expressed in nasopharyngeal carcinomas, and its overexpression inhibits the p-PI3K and p-AKT, lowers elF4B, and encourages cancer cell apoptosis, thereby preventing growth and invasion.

Numerous miRNAs act as oncogenes and activate the PI3K/AKT pathway. For instance, the miR-182 and miR-135b expressed in colorectal cancer tissues are higher than those in surrounding normal tissues. These molecules directly target ST6GALNAC2 and initiate the PI3K/AKT pathway. Accordingly, it has been proposed that the miR-182/-135b/ST6GALNAC2/PI3K/AKT axis could be used as a predictor and potential treatment target for individuals suffering from colorectal cancer [202]. Moreover, patients with colorectal cancer had reduced levels of miR-182 after surgery compared to before surgery. MiR-182 overexpression has been linked to an unfavorable outcome for patients with triple-negative breast cancer. It also increases colorectal cancer cell expansion, migration, and invasion by increasing MMP-2 and MMP-9 levels. Furthermore, miR-182 functions as an oncomiR in colorectal cancer cells by targeting and inhibiting DAB2IP, which may bind with the 3′ UTR of ING5 and facilitate activation of PI3K/Akt/mTOR and Wnt/β-catenin [203]. It has been demonstrated that silencing miR-193 also inhibits EMT mediated by cell proliferation [204].

6.2. PI3K/AKT signaling pathway related lncRNAs in cancer: down and up-regulating role

Studies conducted in silico practically revealed the role of lncRNA 691 in the downregulation of miR-9-5p. Notably, it has been demonstrated that miR-9-5p directly targets PTEN. Therefore, LncRNA 691/miR-9-5p can regulate PTEN expression, which in turn modulates the PTEN/PI3K/AKT signaling in osteosarcoma [205]. According to Cao et al., there is a correlation between a lower patient survival rate and the decreased activity of the lncRNA ADAMTS9-AS2 in gastric cancer. Research has demonstrated that ADAMTS9-AS2 stimulates cell death by modulating the PI3K/Akt pathway and inhibits gastric cancer cell development, progression, and migration. Luo et al. have discovered that TCL6 downregulation is associated with miR-106a-5p upregulation in hepatocellular carcinoma (HCC) tissues. TCL6 up-regulation has been demonstrated to inhibit HCC cell development and migration by binding and silencing miR-106a-5p, releasing PTEN, and preventing AKT phosphorylation and PI3K protein expression [206]. Zhang et al. have found a correlation between reduced LINC00982 levels and tumor size and TNM stage in renal cancer. LINC00982 upregulation inhibited cell growth and elevated cell death in renal cancer cells by modifying PI3K/AKT function [207].

Many oncogenic lncRNAs cause cancer by activating the PI3K/AKT pathway. For instance, Wang et al.'s study has shown that the P13K/AKT pathway is activated in cervical cancer tissues and cell lines with elevated levels of lncRNA RP1-93H18.6. Accordingly, the knockdown of lncRNA RP1-93H18.6 minimized the onset and development of cervical cancer by preventing the PI3K/AKT pathway. According to Qu et al., there is a relationship between increased leukocytes and poor

cytogenetic anomalies, detectable remaining tumor positivity, and a bad outcome with the HOXA-AS2 overexpression in AML patients. Silencing HOXA-AS2 could activate apoptotic cell death, suppress leukemia cell proliferation, decrease phosphorylated PI3K and AKT, and increase P21 and P27 expression [208]. In a study by Wei et al., glioma tissues with elevated levels of BCAR4 were associated with a shorter survival rate and more glioma cell proliferation. BCAR4 accelerates the growth of gliomas by activating the EGFR/PI3K/AKT axis. According to Han et al., a low five-year survival rate among HCC patients is linked to increased levels of CASC11, which is caused by the transcription factor STAT3. It has been demonstrated that CASC11 binds to EZH2 to reduce PTEN expression [209].

6.3. PI3K/AKT signaling pathway related circRNAs in cancer: down and up-regulating role

In vitro studies have discovered modifications in the cellular processes of the circRNA/PI3K/AKT pathway. It has been demonstrated that the knockdown of circRNA cZNF292 in ESCC reduces tumor cell function and promotes cell death. Lower circ0001785 expression has also been found to promote apoptotic cell death and inhibit cell development in osteosarcoma [210].

Research has indicated that in patients with esophageal squamous cell carcinoma (ESCC), low expression of circVRK1 is predictive of poor prognosis [211]. In addition, increased TNM stage and lymph node metastasis (LNM) are strongly correlated with elevated circLPAR3 levels. Circ-EPHB4 expression prevents the advancement of HCC by adversely affecting the HIF-1α/PI3K/AKT and HIF-1α/ZEB1 pathways [167,212]. Circ-ITCH functions as a competing endogenous RNA (ceRNA) for miR-22, which in turn inactivates the PTEN/PI3K/AKT and SP-1 pathways. This is the mechanism by which the expression of circ-ITCH minimizes cellular activities [213].

7. Interaction between ncRNAs and the PI3K signaling pathway in LC

In the context of the PI3K–ncRNAs interactions in LC, the current review generally focuses on the contribution of ncRNAs to the pathogenesis and progression of LC (Tables 1–3), as highlighted in the following sections (Figs. 4–6).

7.1. NcRNAs involved in apoptosis and cell proliferation

Apoptosis is a genetically regulated and evolutionarily conserved process of programmed cell death that is crucial for development and the maintenance of tissue homeostasis in multicellular organisms [214]. This process is vital for eliminating mutated or transformed cells from the body; consequently, the ability to evade apoptosis is regarded as a hallmark of cancer [215]. Survivin, known as an apoptosis inhibitor, is frequently overexpressed in lung adenocarcinomas compared to squamous cell tumors, and studies indicate that elevated expression is associated with reduced survival in NSCLC [216,217].Cell proliferation in cancer denotes the unregulated mechanism through which cancer cells replicate and multiply, resulting in tumor formation and the proliferation of malignant tissues [218]. Increased proliferation and reduced apoptosis are fundamental characteristics of cancer cells, achieved through the modulation of key signaling pathways.

A study discovered that miR-1299 directly targets CDK6 and reduces its expression, reducing liver cancer cell growth [219]. Furthermore, miR-1299 expression dramatically decreased in NSCLC cells and may play a role in NSCLC advancement by targeting EGFR [220]. According to one study, EGFR mutations or abnormal expression can improve cancer cell activities, including development, differentiation, and metastasis [221]. EGFR can increase the expression of p-STAT3, which results in tumor progression [222,223]. Meanwhile, transfecting miR-1299 into A549 and H1975 cells lowered STAT3 expression. These findings indicated that miR-1299 acts as a sponge for EGFR, contributing to the advancement of NSCLC [220]. Furthermore, miR-1299 overexpression reduced PI3K and Akt phosphorylation. 740Y-P, a PI3K agonist, might prevent PI3K downregulation and p-Akt in A549 cells overexpressing miR-1299. Furthermore, 740Y-P effectively inhibited miR-1299-overexpressed A549 cell proliferation, progression, and invasion, suggesting that miR-1299 suppressed NSCLC cell development via the PI3K/Akt signaling pathway [220].

METTL3 is an RNA methyltransferase that regulates mRNA synthesis, destruction, and translation [224]. METTL3 expression has been

Table 1
MiRNAs that are involved in the PI3K signaling pathway in lung cancer.

MiRNAs name	Lung cancer type	Expression	Associated Targeting	Regulation of PI3K signaling	Putative function	Potential application	Ref
MiR-1299	NSCLC	Down	EGFR/PI3K/Akt signal pathway	Inhibition	↑* expression of miR-1299: Inhibits the migration, invasion, EMT, proliferation and promotes the apoptosis	Potential target for the treatment	[220]
MiR-600	LC	Down	METTL3	Inhibition	Inhibits METTL3 expression and suppress cell proliferation, metastasis and elevate apoptosis	Potential target for the treatment	[227]
MiR-210	LUSC	Up	CELF2	Activation	↑ Cell cycle progression ↑ Tumor growth ↑ Proliferation, invasion, and migration	Potential target for patients' prognosis and treatment	[235]
MiR-519d-3p	NSCLC	Down	VEGFA	Inhibition	Suppresses the proliferation, invasion, and Promotes Apoptosis ↓** Levels of Ki67 and N-cadherin Restrained tumor weight and tumor volume	Potential target for therapy	[259]
MiR-485-5p	LUAD	Down	NQO1	Inhibition	↓ Cell migration and proliferation ↑ Apoptosis	Potential target for treatment and diagnosis	[264]
MiR-4732-5p	LUAD	Down	XPR1	Inhibition	Inhibits the migration, invasion, and metastasis	Potential target for treatment	[283]
MiR-15a	NSCLC	Down	Not investigated	Inhibition	Knocking down miR-15a expression: Inhibited the apoptosis of NSCLC cells Promoting the proliferation and invasion	Potential biomarker for diagnosis	[287]
MiR-124-3p	NSCLC	Down	3′-UTR of Rab27a	Inhibition	Inhibit exosome secretion and tumor growth Prevent cell migration, invasion, and metastasis	Potential target for treatment	[293]

↑* indicates the elevation.
↓** indicates the reduction.
Abbreviations: LUSC; lung squamous carcinoma, LUAD; Lung adenocarcinoma, NSCLC; Non-small-cell lung cancer.

Table 2
LncRNAs that are involved in the PI3K signaling pathway in lung cancer.

LncRNAs name	Lung cancer type	Expression	Associated Targeting	Regulation of PI3K signaling	Putative function	Ref
DDX11-AS1	NSCLC	Up	Not mentioned	Activation	Promoting prolifratein Inhibits apoptosis	[240]
TP73-AS1	LUAD	Up	Not mentioned	Activation	↑* Expression of this lncRNAs: Related with poor clinical outcomes Knocking down of this lncRNAs: Inhibits tumor growth and metastasis	[243]
HULC	NSCLC	Up	SPHK1	Activation	↑ Expression of this lncRNAs: Promoting tumor cell proliferation Inhibits apoptosis	[244]
CRNDE	NSCLC	Up	Not mentioned	Activation	Promoting cell proliferation and growth	[247]
WT1-AS	NSCLC	Down	Sponging miR-494-3p	Inhibition	↑ Expression of this lncRNAs: Inhibits cell proliferation, migration and invasion ↑ Cell apoptosis ↑ PTEN expression	[248]
FOXO1	LC	Down	Myc and Cyclin D1	Inhibition	↑ Expression of this lncRNAs: Inhibits cells viability, cell proliferation, colony formation, invasion and metastasis ↑ Cell apoptosis	[249]
FOXD3 (Exosomal lncRNA)	LC	Up	ELAVL1	Activation	↑ Proliferation, invasion, ↑ 5-FU resistance	[266]
TRPM2	NSCLC	Up	MiRNA-138-5p	Activation	↑ Levels of EGFR ↑ Cell proliferation, migration and invasion	[197]
NORAD	NSCLC	Up	MiR-520a-3p	Activation	↑ Proliferation, migration, and invasion ↑ Tumorigenicity and metastasis	[269]
OECC	LC	Up	Not mentioned	Activation	↑ Cell proliferation and metastasis	[271]
TBX5-AS1	NSCLC	Down	Not mentioned	Inhibition	↑ Expression of this lncRNAs: Suppressed cell viability, colony formation, migration, and invasion Promoted apoptosis	[272]
TM4SF1-AS1	LC	Up	Not mentioned	Activation	↑ Expression of this lncRNAs: Promoted the migration and invasion ↓ Expression of E-Cadherin ↑ Expression of Vimentin, Snail and Twist	[305]
LINC00638	NSCLC	Up	MiR-541-3p/IRS1	Activation	↑ Expression of this lncRNAs: ↑ Cells proliferation, growth, migration, and invasion Suppressed apoptosis	[308]

↑* indicates the elevation.
↓** indicates the reduction.
Abbreviations: LUSC; lung squamous carcinoma, LUAD; Lung adenocarcinoma, NSCLC; Non-small-cell lung cancer.

Table 3
CircRNAs that are involved in the PI3K signaling pathway in lung cancer.

CircRNAs name	Lung cancer type	Expression	Associated Targeting	Regulation of PI3K signaling	Putative function	Ref
Circ_0102231	NSCLC	Up	MiR-635/NOVA2	Activation	Knock down of this circRNA: Suppressed cell proliferation and angiogenesis Induced the apoptosis	[251]
CircRPPH1	NSCLC	Up	Not mentioned	Activation	Knock down of this circRNA: Suppressed cell progression Decrease the tumour growth	[273]
Circ_0017639	NSCLC	Up	Not mentioned	Activation	Knock down of this circRNA: Suppressed cell proliferation, migration, and invasion	[10]
Circ_0000376	NSCLC	Up	MiR-488-3p/BRD4	Activation	Downregulation of this circRNA: Suppressed cell proliferation, invasion migration Promoted cell apoptosis and cell cycle arrest	[275]
Circ-ACACA	NSCLC	Up	MiR-1183	Activation	Knock down of this circRNA: Suppressed cell proliferation and migration and glycolysis rate	[253]
Circ-PLCD1	NSCLC	Down	MiR-375 MiR-1179	Inhibition	Suppressed cell proliferation, invasion Promoted apoptosis Elevation of PTEN	[277]

Abbreviations: NSCLC; Non-small-cell lung cancer.

linked to cancer invasion and advancement in lung and colon adenocarcinomas by EGFR upregulation [225,226]. When A549 and H1299 cells were transfected with METTL3, the BAX/BCL-2 ratio increased, indicating that the mitochondrion-mediated apoptotic pathway was activated [227]. Furthermore, it was discovered that miR-600 can target and inhibit METTL3 expression, reversing METTL3's beneficial effect on NSCLC progression. Furthermore, silencing METTL3 reduces the p-AKT/PI3K signaling pathway, increasing mitochondrial apoptosis and suppressing LC cell growth, indicating that miR-600 could be used as a strong LC tumor suppressor in medical applications [227].

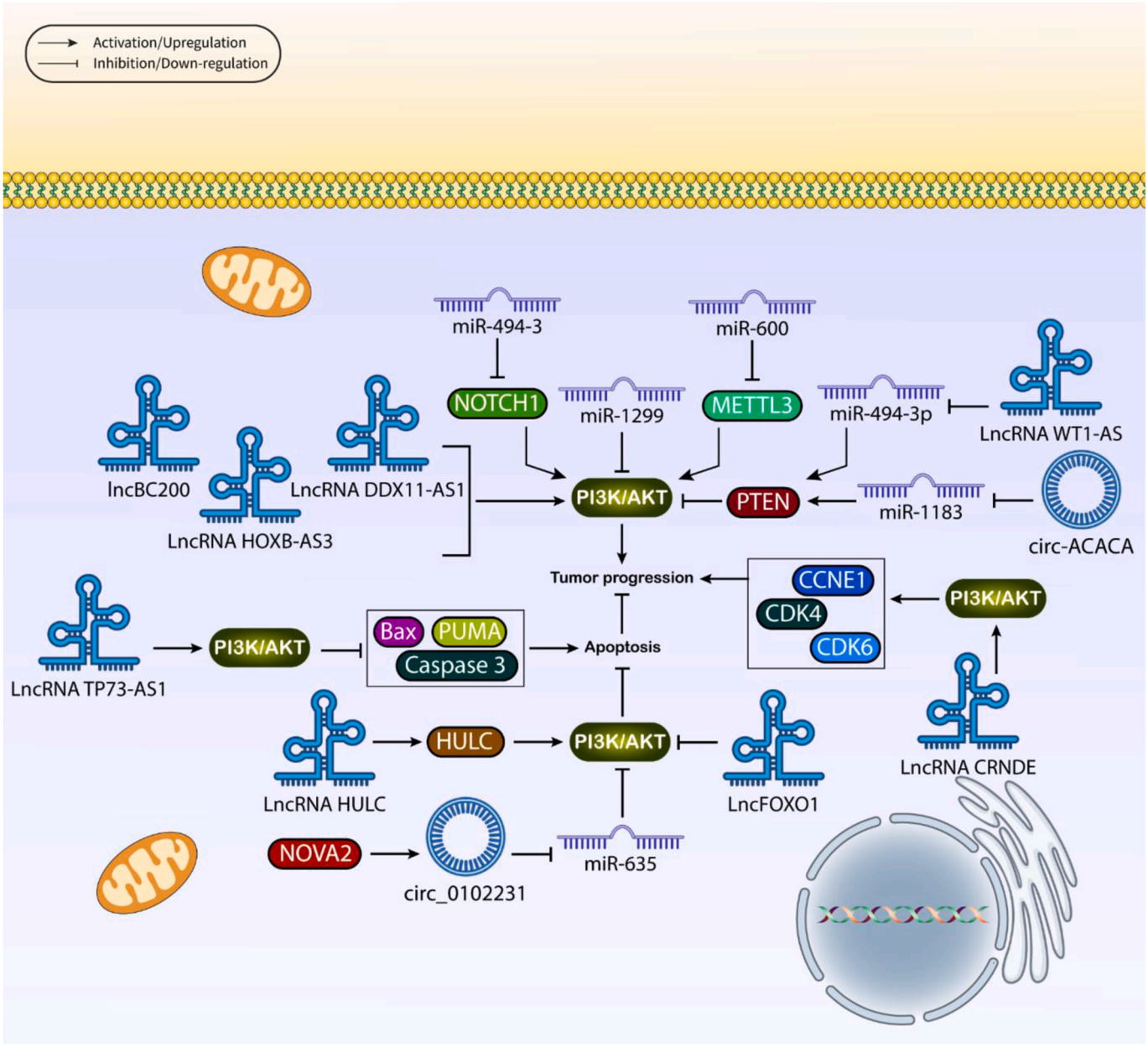

Fig. 4. Schematic view of the relationship between ncRNAs and LC cell proliferation and apoptosis via the PI3K signaling pathway. It highlights how ncRNAs can modulate key components of the PI3K pathway, thereby influencing cellular processes such as growth, proliferation, and apoptosis. Understanding these interactions is vital for elucidating the regulatory mechanisms underlying lung cancer progression and identifying potential therapeutic targets.

MiR-16 plays a key role in the regulation of cell growth, apoptosis, differentiation, and regeneration [228]. Paclitaxel is commonly used in combination with other anti-tumor agents in many chemotherapies to improve LC patients' overall survival (OS) [229]. Chatterjee et al. found that a significant decrease in miR-16 expression is correlated to LC cell resistance to paclitaxel [230]. Increased the PI3K/AKT signaling pathway enhances cancer cell invasion and dissemination via BCL2L2 upregulation [231]. Researchers also discovered that miR-16 regulates BCL-2 in LC cells, leading to chemoresistance in LC. Therefore, concurrently delivering miR-16 and paclitaxel causes caspase-3-induced LC cell apoptosis, overcoming the chemoresistance caused by BCL-2 [230].

Abnormalities in MiR-210-3p expression have been reported in several cancers [232]. CELF2 is a missing region in cancers such as breast cancer (BRCA), low-grade glioma (LGG), and glioblastoma multiforme (GBM) [233] that controls EFNA3 expression to promote tumor progression and angiogenesis [234]. MiR-210-3p was discovered to target CELF2, and knocking out CELF2 accelerated cancer cell development, migration, invasion, and survival [235].

MiR-494 is elevated in NSCLC and has been linked to lymph node metastasis, low tumor differentiation, late-stage tumor, and poor prognosis [236]. Moreover, it has been found that miR-494 can target PTEN, resulting in PI3K/AKT pathway overactivation in various cancers such as liver, colorectal, and lung [118,237,238]. miR-494-3 upregulation in NSCLC patients promotes tumor expansion and dissemination via the NOTCH1/PI3K/AKT pathway and is related to bad outcomes [239]. MiR-494-3p may be a possible biomarker in NSCLC diagnosis and prognosis, as well as a potential target in the regulation of the PI3K/AKT pathway in LC.

LncRNA DDX11-AS1 and lncRNA HOXB-AS3 both have regulatory roles in NSCLC [240,241]. experimental assays showed that overexpression of LncRNA DDX11-AS1 and lncRNA HOXB-AS3 increased

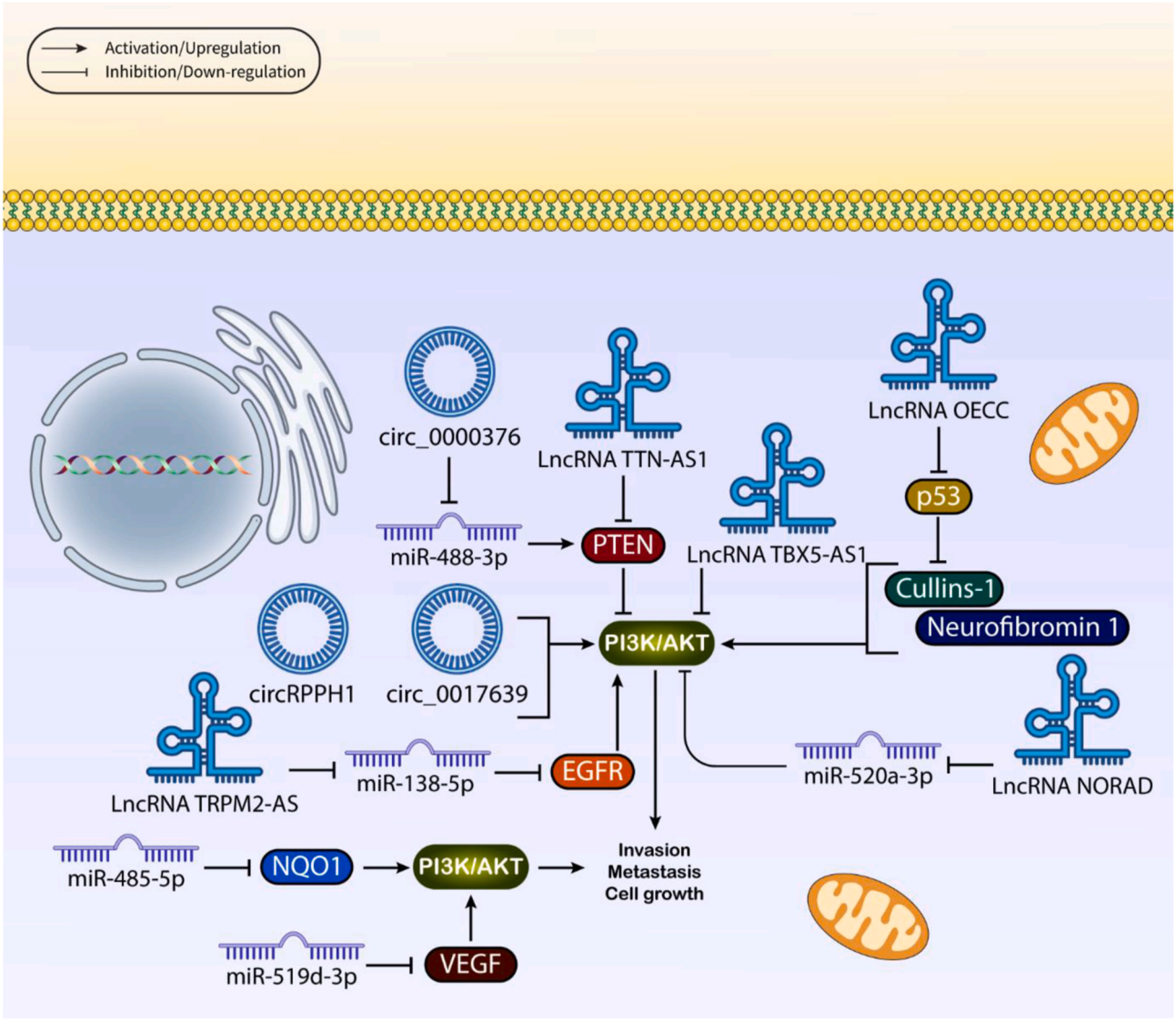

Fig. 5. Schematic view of the relationship between ncRNAs and the LC cell progression, invasion, and migration via the PI3K signaling pathway. It emphasizes the roles of lncRNAs, circRNAs, and miRNAs in regulating key elements of the PI3K pathway, thereby influencing critical processes associated with tumor advancement. By modulating gene expression and signaling cascades, these ncRNAs contribute to the metastatic potential of lung cancer cells.

NSCLC cell proliferation and invasion via activation of the PI3K/AKT signaling pathway [240,241]. Similarly, lncBC200 is upregulated in NSCLC and is linked to poor prognosis and higher TNM staging. Activation of the PI3K/AKT signaling pathway is the main mechanism of lncBC200, which leads to high levels of tumoral growth, cell proliferation, and migration in NSCLC [242]. In addition, LncRNA TP73-AS1 is overexpressed in lung cancer and is related to TNM stage and low survival in lung adenocarcinoma (LAD) patients [243]. The research revealed that knocking down lncRNA TP73-AS1 induced cell cycle arrest; pro-apoptosis proteins include Bax, cleaved caspase 3, and PUMA. In vivo experiments demonstrated that declined levels of lncRNA TP73-AS1 are related to decreased cell invasion and liver metastasis. Western blot assay showed that lncRNA TP73-AS induces its oncogenic effect by enhancing the phosphorylated levels of AKT and PI3K, activating the PI3K/AKT signaling pathway [243]. lncRNA HULC has a carcinogenic role in NSCLC, which is related to worse outcomes and higher stages of cancer. Indeed, lncRNA HULC enhances the levels of sphingosine kinase 1 (SphK1) in NSCLC cells [244]. SPHK1 is an oncogene lipid kinase that regulates cell proliferation, apoptosis, angiogenesis, and cell cycle pathways through managing the production of sphingosine-1-phosphate [245]. SPHK1 induces the PI3K/AKT signaling pathway in cancers through regulation of the phosphorylation levels of AKT in tumoral cells [246]. As a result, upregulation of lncRNA HULC is correlated with restraining apoptosis and improved cell growth through the buildup of SPHK1 and its downstream PI3K/AKT signaling pathway [244]. Furthermore, lncRNA CRNDE promotes NSCLC cell proliferation and growth by advancing the cell cycle from G0/G1 to S phase. Likewise, lncRNA CRNDE can increase CCNE1, CDK4 and CDK6 expression as a result of PI3K/AKT signaling pathway upregulation [247]. LncRNA WT1-AS is another ncRNA that plays an anti-tumorigenic role in NSCLC [248]. According to the explanation, the inhibitory effect of LncRNA WT1-AS in lung cancer is achieved through negative modulation of miR-494-3p, which results in increased levels of cleaved caspase-3 and Bax and decreased levels of CDK2, Bcl-2, and CyclinE1 [248]. Besides, overexpression of miR-494-3p followed by declination of lncRNA WT1-AS in NSCLC is associated with strengthened PTEN levels as the restricted factor of the PI3K/AKT signaling pathway, which contributed to cell growth, invasion, and metastasis in NSCLC [248]. LncFOXO1 is an anti-tumoral agent that plays a regulatory role in NSCLC. Overexpression of LncFOXO1 in NSCLC negatively regulates cell proliferation and increases apoptosis through inhibiting Bcl-2 expression and upregulation of cleaved caspase-3 and Bax [249]. LncFOXO1

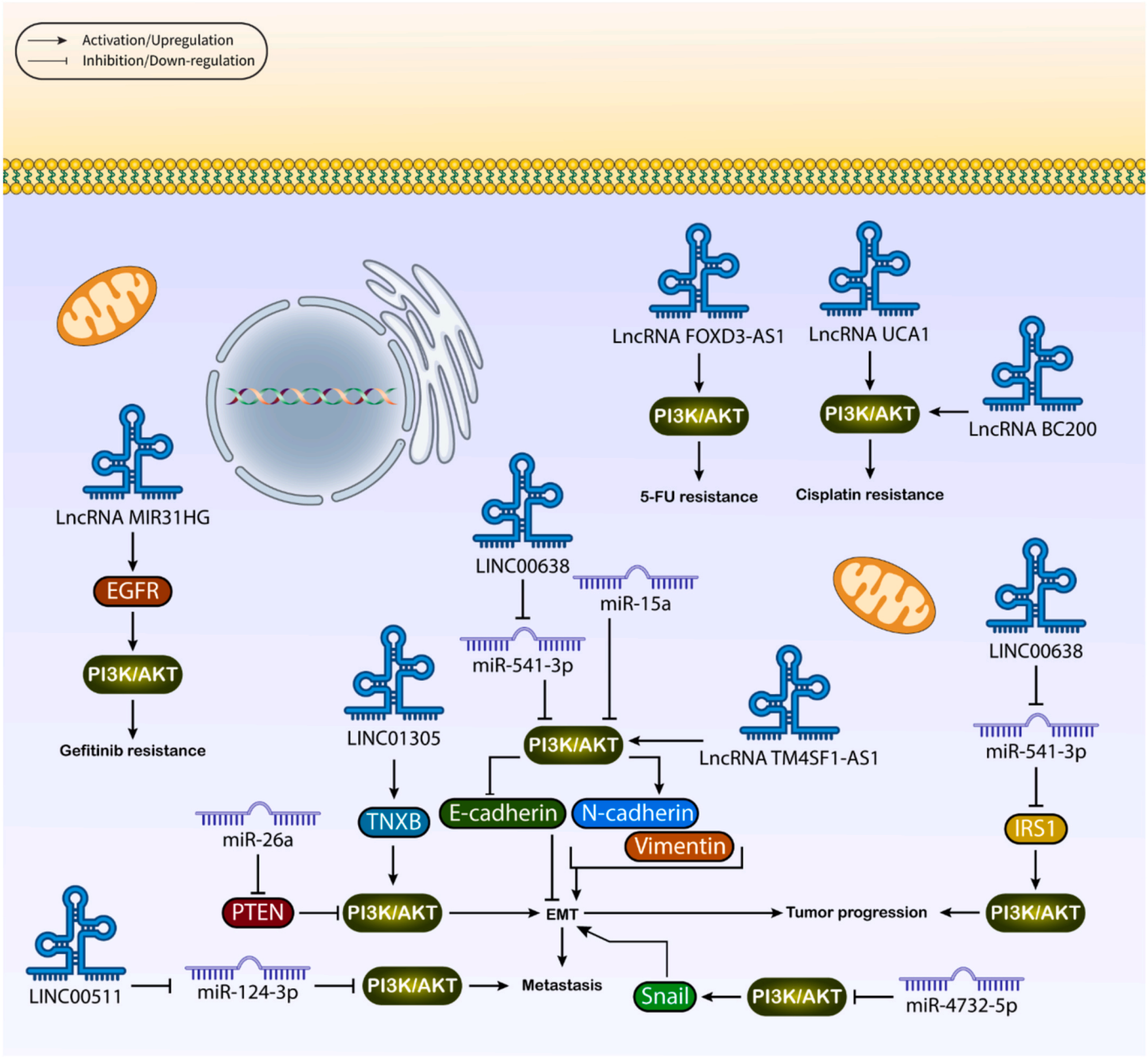

Fig. 6. Schematic view of the relationship between ncRNAs and the EMT process in LC drug resistance via the PI3K signaling pathway.

also downregulates LC cell progression and migration by hindering MMP2 and MMP9 [249]. Moreover, lncFOXO1 could repress lung cancer progression by hindering the phosphorylated PI3K and AKT, which activate the PI3K/AKT signaling pathway. Studies have shown that lncFOXO1 suppressed tumoral growth and c-myc and cyclin-D1 expression by downregulating the PI3K/AKT signaling pathway [249, 250]. Circ_0102231 is one of the ncRNAs in the progression of NSCLC.

Circ_0102231 acts as a sponge for mir-635, increasing PCNA and Bcl-2 levels while decreasing Bax protein levels, resulting in a decrease in apoptosis [251]. The positive regulatory role of circ_0102231 on the PI3K/AKT signaling pathway is induced by the oncogene NOVA2, a member of the NOVA family involved in the progression of NSCLC [251, 252]. It has been demonstrated that NOVA could be regulated by the expression of mir-635 [251]. Overexpression of circ_0102231 regulates the mir-635/NOVA2 mechanism in NSCLC, which increases p-PI3K and p-AKT levels, upregulates cell growth, and restricts apoptotic cell death through the PI3K/AKT signaling pathway [251]. Circ-ACACA as another oncogene is a rise in NSCLC and is associated with cell proliferation through hindering miR-1183 expression [253]. Increased levels of circ-ACACA control the cell growth and invasion in NSCLC by upregulating c-myc protein and MMP-9, respectively [253]. Elevation of c-myc contributes to cell proliferation by promoting the cell cycle phase from G1 to S, and dysregulation of c-myc has been demonstrated to have a role in cancer development [254]. Additionally, MMP-9 regulates cancer progression, migration, and metastasis through the degradation of the extracellular matrix [255]. On the other hand, sponging miR-1183 by circ-ACACA increases PTEN in NSCLC and thus activates the PI3K/AKT signaling pathway [253]. An overview of the several studies on the ncRNA-PI3K signaling pathway in LC and their regulatory mechanisms in apoptosis and cell proliferation was summarized (Fig. 4).

7.2. NcRNAs contributing to invasion and migration

According to research, miR-519 plays a role in LC regulation [256,

257]. Cheng et al. discovered that knocking down LINC01419 could suppress cell growth and invasion in lung ADC by miR-519b-3p overexpression [258]. When compared to the untreated, miR-519d-3p upregulation significantly reduced Ki67 expression, cell survival, and N-cadherin expression while increasing E-cadherin expression in the A549 and NCI-H661 cells containing miR-519d-3p [259]. Also, miR-519d-3p significantly reduced the frequency of VEGF 3-UTR [259]. These findings suggested that miR-519d-3p could target VEGF and prevent p-P38MAPK, p-PI3K, and p-AKT expression, thereby inhibiting LC cell development and migration and promoting apoptosis.

MiR-485-5p has been found to be associated with cancer cell development [260]. NQO1, a quinone inducer, has been found to be overexpressed in a variety of cancers, including lung and breast cancer [261,262]. It has been shown that inhibiting NQO1 inhibits PI3K/Akt pathway activation [263], whereas suppressing miR-485-5p induces Akt and PI3K phosphorylation [264], implying that the miR-485-5p/NQO1 axis controls NSCLC progression via the PI3K/Akt pathway [265].

The lncRNA FOXD3-AS1 is linked to the development of NSCLC via exosomes. lncRNA FOXD3-AS1 controls the cell functions through an RNA binding protein called ELAVL1 [266,267]. Experiments on exosomes derived from lung cancer cells revealed that lncRNA FOXD3-AS1 increases PI3K and AKT phosphorylation, which induces the PI3K/AKT signaling pathway in cells [266]. Interestingly, the lncRNA TRPM2-AS plays an oncogenic role in NSCLC by increasing the expression of mutated EGFR [197]. EGFR is a target protein of miR138-5p that regulates the PI3K/AKT signaling pathway [197]. Mutation of the EGFR tyrosine kinase domain activates the AKT pathway, resulting in tumor growth and invasion in NSCLC [268]. Researchers discovered that the lncRNA TRPM2-AS promotes NSCLC progression by inhibiting miR138-5p levels, which eventually leads to EGFR augmentation. These findings have enabled the development of new target therapy methods for the treatment of NSCLC patients [197]. Wan et al. discovered that lncRNA NORAD is one of the ncRNAs that controls the progression of NSCLC cells by targeting miR-520a-3p [269]. According to previous studies, the expression of miR-520a-3p in NSCLC inhibits cell proliferation by hindering the expression of p-mTOR, pAKT, and p-PI3K [270]. Cellular assays showed that lncRNA NORAD reversed the action of miR-520a-3p by inhibiting its function, which leads to the induction of cell proliferation and migration in NSCLC through overexpression of proteins involved in the PI3K/Akt signaling pathway [269]. Based on another study, lncRNA OECC expression is increased in NSCLC and is positively linked to cell proliferation and cell migration [271]. High levels of lncRNA OECC cause an increase in the expression of mRNAs of PI3K, Akt, 5′-AMP-activated protein kinase, and phosphoinositide-dependent kinase-1 endothelial nitric synthase [271]. However, lncRNA OECC negatively decreases the expression of tumor p53, a regulator of cullins-1 and neurofibromin 1. As a result, the PI3K/Akt signaling pathway is activated, which leads to the progression of NSCLC [271]. Furthermore, the lncRNA TBX5-AS1 has an anti-tumoral function in NSCLC patients. Downregulation of the lncRNA TBX5-AS1 is linked to advanced NSCLC and a poor prognosis [272]. The experimental assay revealed that inhibited lncRNA TBX5-AS1 is associated with decreased BAX and increased Bcl-2, resulting in the inhibition of apoptosis and tumor growth [272]. More research revealed that the lncRNA TBX5-AS1 suppresses cell progression and migration in NSCLC by reducing PI3K/AKT signaling pathway phosphorylation in lung cancer [272].

QRT-PCR assays revealed that circRPPH1 functions as an oncogene in NSCLC. Cell culture and in vivo experiments revealed that circRPPH1 expression promotes cell progression and invasion in NSCLC by upregulating the PI3K/AKT signaling pathway [273]. Circ_0017639 is another ncRNA that is overexpressed in NSCLC. Zhang et al. demonstrated that circ_0017639 promotes NSCLC cell growth and invasion by modulating the p-PI3K and p-AKT pathways [10]. The use of SC97 as an AKT activator in knocked-down circ_0017639 cells increases NSCLC proliferation and migration via PI3K/AKT signaling pathway reactivation [10,274]. Furthermore, circ_0000376 acts as an oncogene in NSCLC. According to recent research, circ_0000376 reduces apoptosis and stops cells in the G0/G1 phase by hindering the function of miR-488-3p [275]. Indeed, suppression of miR-488-3p increased the levels of BRD4 [275]. BRD4, as one of the bromodomain and extra terminal (BET) protein families, acts as a regulator of oncogenes in cancers through controlling the transcription process and DNA retention [276]. Circ_0000376 hindered the expression of PTEN through sponging miR-488-3p, which resulted in a rise of phosphorylated levels of PI3K and AKT in NSCLC [275]. Activation of the PI3K/AKT signaling pathway by circ_0000376 positively increases the invasion, migration, and growth of NSCLC cells [275]. On the other hand, circ_PLCD1 is one of the target genes transactivated by p53 to regulate cell proliferation and apoptosis [277]. In human cancers, the anti-tumoral function of p53 is impaired, and mutation of p53 can result in cell proliferation and tumor growth [278]. Circ_PLCD1 suppresses tumors and activates PTEN by sponging miR-375 and miR-1179 [277]. Thus, the knockdown of circ-PLCD1 is associated with tumor progression and lower survival [277]. On the contrary, lncRNA TTN-AS1 promotes cell growth and invasion in lung adenocarcinoma by stabilizing PTEN protein and activating the PI3K/AKT signaling pathway [279]. Several ncRNAs that interact with PI3K signaling in LC invasion and migration progression were summarized in Fig. 5.

7.3. NcRNAs affecting epithelial-to-mesenchymal transition and metastasis

Mutations in the XPR1 gene, which encodes an inorganic phosphate exporter, have recently been found in patients with primary familial brain calcification [280]. Notably, recent research has found a link between XPR1 expression levels and certain biological events. For example, XPR1 facilitates NF-kB signaling phosphorylation and activation, which is essential for XPR1-mediated cancer-promoting functions in tumor samples [281]. MiR-4732-5p has been shown to suppress the development of NSCLC [282]. The increased levels of MiR-4732-5p could bind to XPR1 and inhibit NSCLC infiltration, invasion, angiogenesis, and EMT. Furthermore, miR-4732-5p inhibits aggregation and migration in response to EGF stimulation by affecting N-cadherin, vimentin, and E-cadherin. Increased miR-4732-5p levels also inhibited p-Akt and p-GSK3b levels in A549 cells when stimulated with EGF, but not overall Akt and GSK3b levels. MiR-4732-5p only inhibited EMT via the Snail protein and could be altered by XPR1 overexpression but did not affect Twist, Slug, Zeb1, or Zeb2. These findings support the idea that miR-4732-5p prevents EMT via the PI3K/Akt/GSK3b/Snail pathway [283].

MiR-15 family members act as tumor suppressors in several malignancies [284,285]. MiR-15a, which targets Bcl2, has been shown to induce apoptosis in CLLs [286]. One study found that miR-15a expression was significantly lower in NSCLC tissues, implying that low levels of miR-15a expression may contribute to the development of NSCLC. MiR-15a silence increased the expression of Bcl2, p-ERK, and p-AKT while decreasing the expression of apoptotic proteins in NSCLC cells. As a result, miR-15a has the potential to be a new tumor suppressor in NSCLC, regulating biological activity via the PI3K/AKT and MAPK signaling pathways [287]. Pouliot et al. found that miR-15 induced chemosensitivity in resistant tumor cells by regulating Wee1 and CHK1 expression [288]. In addition, the mir-15 family regulates the EMT process, which influences cancer cell metastasis [289,290]. It has been found that inhibiting miR-15a expression in NSCLC cells increased the expression of vimentin, N-cadherin, and slug while decreasing the expression of E-cadherin. These findings suggest that low miR-15a levels may promote EMT by regulating E-cadherin and vimentin in cancer cells [287].

Many investigations have shown that Rab27a can regulate cancer-derived exosome release and metastasis and that knocking down Rab27a decreases exosome secretion, cancer cell proliferation, and

invasion in melanoma and colorectal cancer [291,292]. Furthermore, overexpressed miR-124-3p has been associated with tumor development and progression. MiR-124-3p can target Rab27a and suppress NSCLC cell migration and exosome release. MiR-124-3p also could act as a tumor suppressive agent in lung cancer through the regulation of the PI3K/AKT signaling pathway [293]. Furthermore, LINC00511 promoted NSCLC exosome release, cell growth, and invasion by downregulating miR-124-3p. The increased expression of LINC00511 causes it to act as a ceRNA for miR-124-3p, suppressing miR-124-3p regulation and promoting NSCLC metastasis. These findings revealed interactions between miRNA, mRNA, and lncRNA, implying that miR-124-3p may play a role in the advancement and metastasis of NSCLC [293].

MiR-92a has been discovered to function as an oncogene in a variety of tumors, primarily by inhibiting PTEN [294–296]. Ke et al. found that miR-92a promotes colorectal cancer cell metastasis by inhibiting PTEN and thus increasing PI3K/AKT pathway activation [297]. MiR-was found to be upregulated in NSCLC and directly regulated PTEN, resulting in increased l growth, metastasis, and chemoresistance [228]. Furthermore, F-box/WD repeat-containing protein 7 (FBXW7) is a tumor suppressor that is regulated by miR-92a, suggesting that miR-92a could be used as an approach in the treatment of NSCLC [298].

According to several studies, miR-26a has a dual function as a tumor suppressor or oncogene in various cancers. For example, miR-26a has been shown to inhibit the development of breast cancer, liver cancer, and nasopharyngeal carcinoma [299–301], while increasing glioma cell proliferation by targeting PTEN [302]. Wang et al. discovered an increase in miR-26a expression in NSCLC, which is linked to increased NSCLC progression and invasion by PTEN inhibition and the PI3K/AKT pathway activation [303]. Concerning mir-26a′s oncogenic role in LC, Xu et al. demonstrated that miR-26a promotes NSCLC cell proliferation and drug resistance to EGFR-TKI by inhibiting protein tyrosine phosphatase non-receptor type 13 (PTPN13), a tumor suppressor in NSCLCs [304]. As a result, Src phosphorylation and activation continue, activating the EGFR pathway.

LncRNA TM4SF1-AS1 is one of the ncRNAs that specifically increase the metastasis and invasion of lung cancer cells by regulating the EMT mechanism [305,306]. More investigations revealed that lncRNA TM4SF1-AS1 expression increases the levels of p-PI3K, PDK1, mTOR, and p-mTOR in lung cancer, which results in PI3K/AKT signaling pathway activation [305]. Upregulation of the PI3K/AKT signaling pathway promotes EMT by decreasing E-cadherin and increasing Vimentin, Snail, and Twist (as mesenchymal cell markers), which is related to cell migration and metastasis in lung cancer [305]. Similarly, Yan et al. discovered that the lncRNA LINC01305 is linked to TNM staging, tumor development, and metastasis via an increase in the EMT pathway via the TNXB-mediated PI3K/Akt signaling pathway. qRT-PCR data revealed that the lncRNA LINC01305 is overexpressed in patients with advanced lung cancer and is associated with a poor overall survival [307]. In like manner, lncRNA LINC00638 enhances cell proliferation and migration in NSCLC through the EMT pathway [308]. lncRNA LINC00638 restrains the E-cadherin and induces N-cadherin and vimentin levels in lung cancer cells. Western blot assays revealed high production of lncRNA LINC00638 increases pro-cell cycle markers cyclin D1, cyclin E1, and their complex formation proteins like CDK2, and CDK4 levels. Also, inhibitors of cyclin-CDK complexes like p21 and p27 are decreased, followed by upregulation of lncRNA LINC00638 [308]. The mechanism of lncRNA LINC00638 to develop NSCLC and activation of the PI3K/Akt signaling pathway is to repress the function of miR-541-3p [308]. Downregulation of miR-541-3p is associated with overexpression of insulin receptor substrate 1 (IRS1), an intermediate protein that activates cell growth promoters and influences tumor progression [309]. Recent studies showed that phosphorylation of IRS1 leads to the activation of the PI3K/Akt signaling pathway [310]. As a result, LINC00638 promotes NSCLC progression by sponging miR-541-3p, which causes IRS1/PI3K/Akt pathway upregulation [308]. A summary of ncRNAs that promote EMT and metastasis in LC through the PI3K/AKT signaling pathway is shown in Fig. 6.

7.4. Non-coding RNAs in drug resistance

In recent years, advances in the discovery of various mutations involved in the progression of NSCLC have resulted in the emergence of new targeted therapy techniques [311]. However, due to gene diversity, alterations, and drug resistance, the prognosis of NSCLC patients remains difficult. To date, numerous mechanisms and pathways of resistance to chemotherapy agents have been discovered [312]. NcRNAs play a role in cancer drug resistance by regulating various mechanisms such as cell proliferation and apoptosis, the EMT pathway, and drug delivery [313].

Platinum-based drugs, such as cisplatin, are one of the most commonly used chemotherapy agents in lung cancer treatment because they crosslink to DNA, preventing DNA repair in cancer cells and promoting apoptosis [314]. LncRNA ROR is one of the ncRNAs that influences the cisplatin response in lung cancer. In NSCLC, lncRNA ROR overexpression correlates with tumor growth, invasion, and cisplatin resistance via suppressing apoptosis and increasing the PI3K/AKT signaling pathway [315]. Indeed, upregulation of the lncRNA ROR increases the levels of bcl-1, PI3K, Akt, and mTOR while decreasing the levels of bax. Overall, lncRNA ROR knockdown appears to be effective in reducing cisplatin resistance in lung cancer cells by downregulating the PI3K/AKT signaling pathway [315]. Similarly, the upregulation of lncRNA BC200 in NSCLC is associated with cisplatin resistance by modulating apoptosis in lung cancer cells through the PI3K/AKT signaling pathway [242].

Gefitinib belongs to the tyrosine kinase inhibitor class, and it inhibits the function and signaling pathway of EGFR in tumor cells. Gefitinib can improve survival in patients with EGFR mutations and advanced stages of lung cancer and is used as a treatment strategy for lung cancer patients [316]. LncRNA MIR31HG overexpression in NSCLC is associated with gefitinib resistance and cancer progression through upregulation of p-EGFR, p-PI3K, and p-AKT levels and restrains P53 expression. Wang et al. revealed that silencing lncRNA MIR31HG in PC9-R cells increases the sensitivity to gefitinib therapy through the EGFR/PI3K/AKT pathway [317]. On the other hand, apoptosis is inhibited in saturated lncRNA MIR31HG cells by increasing Bcl-2 levels while decreasing Caspase-9, Caspase-3, and Bax proteins [317].

5-fluorouracil (5-FU) acts as an anti-cancer drug by preventing DNA replication during the cell cycle by inhibiting thymidylate synthase. In addition to other drugs, 5-FU is used as a chemotherapy strategy in cancer patients [318,319]. As previously discussed, the lncRNA FOXD3-AS1 is upregulated in lung cancer and is linked to cell development and invasion. Exosomes transfected with the lncRNA FOXD3-AS1 induce 5-FU resistance in lung cancer by suppressing apoptosis and maintaining cell proliferation by activating the PI3K/AKT pathway [266]. Fig. 6 shows the drug resistance and the effect of some of the ncRNAs through the regulator of the PI3K/AKT signaling pathway in LC cell invasion and the EMT process.

8. NcRNA and clinical application: therapeutic target and as diagnosis/prognosis biomarkers

NcRNAs have enormous therapeutic value as important mediators of LC development [320]. Patients can target oncogenic ncRNAs to enhance their LC treatments. Increased miR-96-5p levels in LC samples were found to upregulate Bax, MMP9, and Bcl-2 levels, allowing H1299 cell development and aggression [321]. Similarly, lncRNA MNX1-AS1 was found to be significantly overexpressed in LC patients, and its silencing inhibited the proliferative, migratory, and invasive capacity of LC cells by myosin IG activation [322]. Furthermore, Gao et al. demonstrated that the lncRNA FAM138B acts as a sponge for miR-105-5p, reducing NSCLC cell expansion and aggression [323]. In addition, researchers discovered that upregulated circANKRD28 could

increase SOCS3 expression via miR-221-3p sponging, leading to increased sensitivity to cisplatin in NSCLC cells [324]. In summary, therapeutic methods that target oncogenic ncRNAs or induce tumor-suppressive ncRNAs will contribute significantly to the advancement of personalized LC therapies.

There are few potent diagnostic or predictive screening methods for the vast majority of LC patients with a bad prognosis [325]. NcRNAs have been discovered to have diverse expression structures, to be very stable and specific, and to be detectable [225,226,326,327]. MiRNAs have distinct characteristics that make them useful as predictors for LC patients. Wang et al. discovered that high miR-21 levels were significantly related to OS in LC patients, with an AUC of 0.87 [225].

It has been demonstrated that PI3K/AKT-related ncRNAs are potential biomarkers in cancer diagnosis and prognosis. Patients with bladder cancer, breast cancer, glioma, and ovarian cancer with bad prognosis had down-regulated miR-125b-3p, miR-320, miR-126, miR-337–3p, and miR-149, respectively [194,201,328–330]. On the other hand, liver cancer patients with a low survival rate overexpressed miR-494-3p [331]. In addition, TINCR, H19, and LINC00265 have diagnostic power values in colorectal cancer, breast cancer, and AML patients, respectively [332–334]. Overexpression of several lncRNAs, including HOXA-AS2, HOTTIP, and MALAT1, could also be used to predict low cancer-related survival [208,335,336].

The FDA and/or the European Medicines Agency (EMA) have approved 11 RNA-based therapies aimed at targeting gene alterations in the liver, muscle, or central nervous system. All of these therapies are siRNAs or ASOs that produce particular gene downregulation or ASOs that inhibit pre-mRNA splicing. Furthermore, a slew of RNA medicines are in phase II or III clinical trials, including novel molecules like miRNA mimics and antimiRs, but no lncRNA-based therapies are currently in the clinic [337,338]. LncRNAs and circRNAs are also used in trials for LC. Yuan et al. discovered that CRNDE and TA73-AS1 levels in plasma were substantially elevated in NSCLC tissues, with AUCs for differentiating NSCLC of 0.822 and 0.815, respectively [326]. According to Zhang et al., the level of NPSR1-AS1 in LUAD samples was significantly higher than in non-malignant samples and was positively correlated with OS [339]. Zou et al. also found that serum circERBB2 had a higher AUC than AUC for CYFRA21-1 and CEA in NSCLC differentiation [340].

9. Conclusion

NcRNAs are part of a complex regulatory system that regulates several signaling pathways in cancer. This review found that lung cancer is a complicated disease with previously unknown regulators. We investigated the most recent studies on several ncRNAs and their functions in the PI3K/AKT/mTOR signaling cascade, which has been linked to the development of NSCLC. MiRNAs can regulate gene transcription, resulting in cancer prevention or progression. CircRNAs and lncRNAs function as miRNA sponges, either promoting or suppressing NSCLC. Down- or overexpressed ncRNAs can help diagnose patients with early or late-stage lung cancer. PI3K/AKT-related ncRNAs have been identified as promising candidates for cancer diagnosis and prognosis. Given the biological relationship between ncRNAs, it appears that combining multiple of these transcripts will be advantageous in building high-accuracy predictor panels. Furthermore, regulating ncRNA levels can help with method selection and treatment efficacy prediction. Furthermore, ncRNA affects the activated PI3K/AKT/mTOR pathway, which regulates tumor cell sensitivity to chemo- and endocrine-based therapy. ncRNAs also alter the mechanism of EMT and the features of cancer stem cells by influencing PTEN expression levels and other EMT-related genes, resulting in aggressive, invasive, and relapse-prone cancer. Because a single RNA molecule can affect many gene expressions, additional study should focus on identifying communication between ncRNAs that correspond to cancer promoters or inhibitors. LncRNAs regulate the activity of the PI3K/AKT pathway through a variety of mechanisms, one of which is a competition endogenous RNA for microRNAs. As a result, the biological relationship between these two forms of ncRNAs provides a well-established method for activating or inhibiting this pathway. Potential targeted therapeutics that target the PI3K/AKT pathway while avoiding interference with other signaling pathways should take into account the complex interactions between miRNAs and lncRNA. In addition, more clinical trials are needed to evaluate the side effects and efficacy of ncRNA-based therapy in NSCLC patients. Finally, the use of ncRNA inhibitors or mimics in combination with conventional chemotherapy, immunotherapy, or targeted therapy should be studied.

CRediT authorship contribution statement

Mehrdad Hashemi: Writing – original draft, Conceptualization. **Asal Abolghasemi Fard:** Writing – original draft, Conceptualization. **Bita Pakshad:** Writing – original draft, Conceptualization. **Pezhman Shafiei Asheghabadi:** Writing – original draft, Conceptualization. **Amineh Hosseinkhani:** Writing – original draft, Conceptualization. **Atena Sadat Hosseini:** Resources, Investigation. **Parham Moradi:** Resources, Investigation. **Mohammadreza Mohammadbeygi Niye:** Resources, Investigation. **Ghazal Najafi:** Visualization. **Mohadeseh Farahzadi:** Visualization. **Saloomeh Khoushab:** Visualization. **Afshin Taheriazam:** Supervision. **Najma Farahani:** Supervision. **Mahya Mohammadi:** Supervision. **Salman Daneshi:** Writing – review & editing. **Noushin Nabavi:** Writing – review & editing. **Maliheh Entezari:** Supervision.

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