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The NcRNA/Wnt axis in lung cancer: oncogenic mechanisms, remarkable indicators and therapeutic targets

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Abstract

Early diagnosis of lung cancer (LC) is challenging, treatment options are limited, and treatment resistance leads to poor prognosis and management in most patients. The Wnt/β-catenin signaling pathway plays a vital role in the occurrence, progression, and therapeutic response of LC. Recent studies indicate that non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) function as epigenetic regulators that can promote or inhibit Wnt/β-catenin signaling by interacting with Wnt proteins, receptors, signaling transducers, and transcriptional effectors, thereby affecting LC cell proliferation, metastasis, invasion, and treatment resistance. Deepening our understanding of the regulatory network between ncRNAs and the Wnt/β-catenin signaling pathway will help overcome the limitations of current LC diagnosis and treatment methods. This article comprehensively reviews the regulatory mechanisms related to the functions of ncRNAs and the Wnt/β-catenin pathway in LC, examining their potential as diagnostic and prognostic biomarkers and therapeutic targets, aiming to offer new promising perspectives for LC diagnosis and treatment.

Keywords Lung cancer, Wnt/β-catenin, ncRNAs, Mechanism, Biomarkers

Introduction

Lung cancer (LC) is the most common malignant tumor worldwide. Recent global epidemiological data show that there were approximately 2.5 million new LC cases in 2022, accounting for one in eight (12.4%) of all new cancer cases [1]. Despite advances in oncology, critical challenges persist in LC interception: (1) incomplete characterization of molecular drivers during carcinogenesis, (2) absence of robust early diagnostic biomarkers, (3) therapeutic limitations exacerbated by acquired resistance mechanisms [2, 3]. These unmet needs highlight the imperative to delineate pathogenic molecular events and identify novel diagnostic/therapeutic targets.

Emerging evidence implicates dysregulated Wnt/β-catenin signaling as a central mediator of non-small cell lung cancer (NSCLC) progression and chemoresistance

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[4]. Notably, 70% of lung adenocarcinoma (LUAD) specimens exhibit aberrant Wnt pathway activity, with microenvironmental Wnt activation observed in 80% of cases [5]. Paradoxically, canonical mutations in β-catenin and APC remain infrequent (< 20%) in LC patients, suggesting alternative regulatory mechanisms [6, 7]. This paradox has shifted scientific focus toward epigenetic regulators, particularly non-coding RNAs (ncRNAs) that orchestrate multilevel gene regulation [8].

NcRNAs have diverse biological regulatory functions, including modifying the stability and translation of cytoplasmic mRNA, disrupting signaling pathways, regulating chromatin activity, and managing the formation of membrane-less organelles [9–12]. Recent research indicates that ncRNAs in LC can act as oncogenes or tumor suppressors by modulating the Wnt/β-catenin signaling pathway, suggesting that targeting ncRNAs is a promising therapeutic approach [13–15]. Moreover, ncRNAs exhibit high stability in the body fluids of LC patients and show tissue-specific expression in LC, making them excellent candidates as diagnostic and therapeutic biomarkers [16–18]. Although previous studies have explored the roles of ncRNAs (such as lncRNA, miRNA, and circRNA) in LC, these investigations often focus on a single type of ncRNA or isolated signaling pathways, lacking a systematic understanding of the regulatory network between ncRNAs and the Wnt signaling pathway, and the mechanistic links between pathway dysregulation and clinical phenotypes remain unclear. Therefore, this review comprehensively investigates how multiple types of ncRNAs regulate the Wnt/β-catenin axis to collectively influence the onset and progression of LC, within the framework of "molecules (ncRNAs) → pathway hub (Wnt/β-catenin) → disease phenotype (LC)." Furthermore, the review explores the clinical translational pathway for ncRNAs, addressing three key stages: "early diagnostic biomarkers → dynamic prognostic assessment → precise therapeutic targets", aiming to provide new insights into early diagnosis, prognosis, and novel treatment strategies.

Classification, characterization, and biological functions of NcRNAs

Over the past few decades, it has become increasingly recognized that ncRNAs play fundamental roles in regulating post-transcriptional modifications of mRNA, controlling target gene expression, modulating signaling pathways, and determining cell fate [19–21]. Based on their size, ncRNAs can be further classified into subtypes, such as miRNAs, lncRNAs, and circRNAs [22]. MiRNAs are endogenously expressed non-coding RNAs that are approximately 21–23 nucleotides (nt) in length. As key regulatory elements, miRNAs bind to complementary target mRNAs to inhibit protein translation and play an important role in the regulatory mechanisms of various organisms. The main mechanisms of miRNA action can be divided into two categories: 1) miRNAs bind to the open reading frame (ORF) of mRNA, forming a double-stranded structure that leads to mRNA degradation; and 2) miRNAs pair with complementary sequences in the 3' UTR of mRNAs, inhibiting post-transcriptional translation [23–25]. LncRNAs generally refer to non-coding RNAs longer than 200 nt. They can participate in various biological processes, such as the reprogramming of pluripotent stem cells, tumor progression, and cell cycle regulation, through multiple modes of action, including signaling, decoying, guiding, and scaffolding [10, 26]. CircRNAs are a type of non-coding RNA molecule characterized by a circular structure due to covalent bonding, lacking both a 5' cap and a 3' poly(A) tail [27]. CircRNAs can function as miRNA sponges, transcriptional regulators, and protein scaffolds, contributing to tumorigenesis, proliferation, metastasis, and drug resistance [28, 29]. Recent studies indicate that ncRNAs and their key signaling pathways play a crucial role in the phenotype and progression of LC [30–32].

The Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway, or canonical (β-catenin-dependent) pathway, is a vital cellular signaling mechanism that plays a crucial role in embryonic development, cell proliferation, differentiation, and the maintenance of stem cell characteristics. Activation of this pathway typically involves the binding of Wnt proteins to Frizzled (FZD) receptors located on the cell membrane, which subsequently modulates intracellular β-catenin levels [33, 34]. The activation of this pathway can be divided into three steps: (1) at the cell membrane, Wnt proteins bind to Frizzled receptors and activate the low density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) co-receptors; (2) in the cytoplasm, this process triggers the Dishevelled (DVL)-mediated dissociation of the β-catenin destruction complex (DC), which consists of AXIN, APC, GSK-3β, and CK-1α, leading to the loss of its ability to degrade β-catenin; and (3) in the nucleus, β-catenin binds to transcription factors, promoting the transcription of target genes involved in cell proliferation and fate determination [35, 36]. When the Wnt/β-catenin pathway is inactive, DC leads to the phosphorylation of β-catenin by CK1α and GSK3β, followed by its degradation by the proteasome [37] (Fig. 1).

The Wnt/β-catenin signaling pathway in LC

The Wnt/β-catenin signaling pathway is a key regulator of lung homeostasis; however, its complex dysregulation is a significant factor in the occurrence and progression of LC. This pathway not only governs the carcinogenic process but also regulates tumor stem cell properties, resistance, and cellular dormancy, invasion, and metastasis

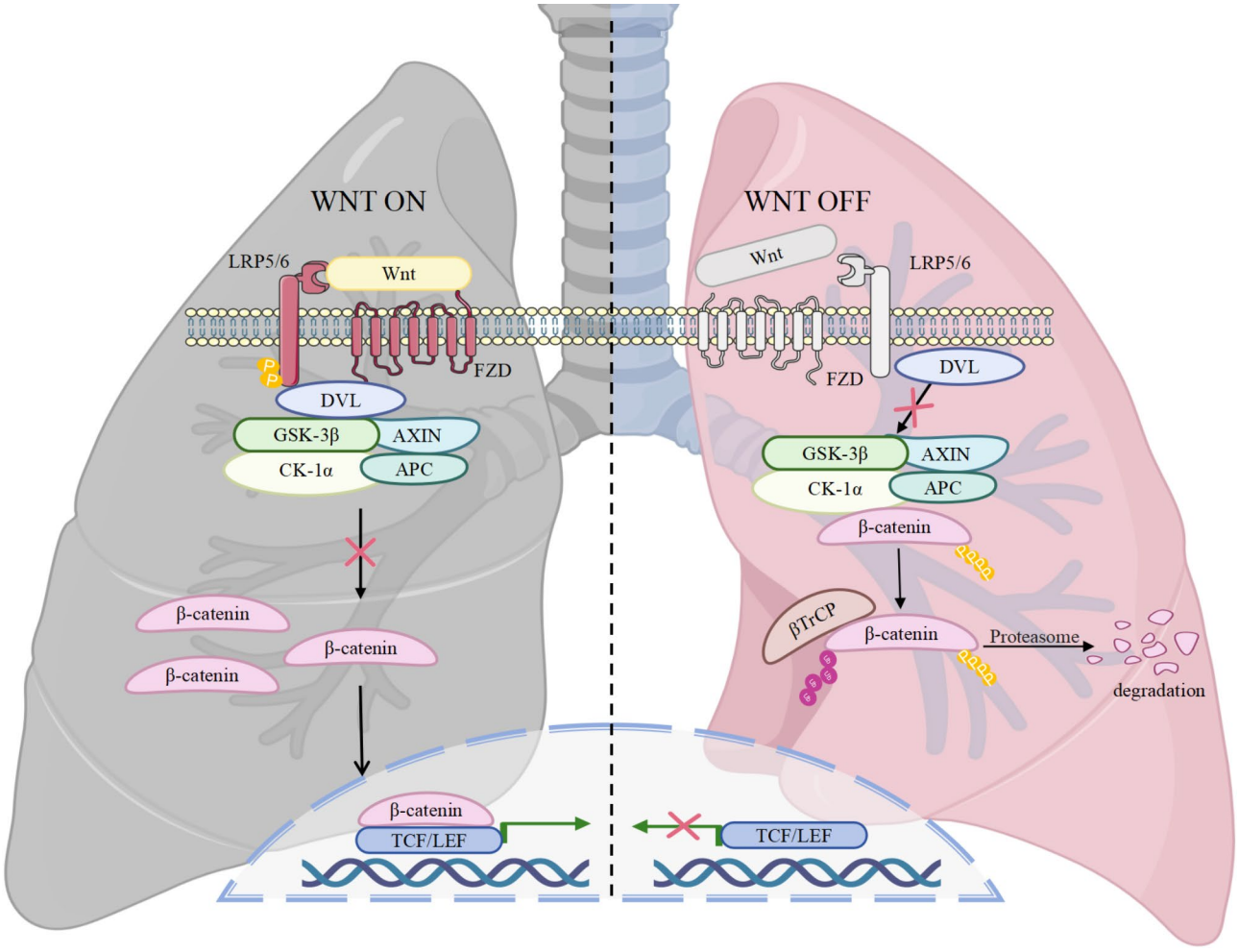

Fig. 1 Wnt/β-catenin signaling pathway. When the Wnt pathway is activated, Wnt ligands are recognized by FZD and LRP5/6. This leads to the recruitment of AXIN and GSK-3β to the cell membrane by activated DVL, causing the disassembly of the β-catenin destruction complex and removing its ability to degrade β-catenin. Subsequently, β-catenin translocates from the cytoplasm to the nucleus, where it activates its target genes by interacting with TCF/LEF. When the Wnt/β-catenin pathway is inactive, the β-catenin destruction complex, composed of AXIN, APC, GSK-3β, and CK-1α, leads to the phosphorylation of β-catenin by CK1α and GSK3β, followed by its degradation by the proteasome

[5, 38–40]. The canonical Wnt signaling pathway is a key driver of lung carcinogenesis, and aberrant activation of the Wnt signaling pathway is significantly correlated with tumor initiation potential [4, 41, 42]. It has been shown that the aberrant expression of FZD3, FZD8, and FZD9 is closely linked to the evolution of NSCLC [38]. In addition, upregulation of pathway regulators, such as WNT3, DLV3, AXIN, and β-catenin, activates WNT/β-catenin signaling to induce tumorigenesis in healthy cells [43].

The Wnt signaling pathway is closely related to LC metastasis. The simultaneous activation of the canonical Wnt pathway associated with other oncogenic pathways in the lung epithelium including Kras, leads to a more aggressive tumor phenotype, characterized by reduced E-cadherin expression and the induction of an embryonic distal progenitor cell phenotype [44]. Wnt2b and Wnt5a promote tumor progression in NSCLC by inducing M2 tumor-associated macrophages (TAMs), resulting in more aggressive behavior [45]. Similarly, overexpression of Wnt1 [46] and Wnt3 [47] may be associated with the development of more aggressive tumors.

The cytoplasmic-nuclear translocation of β-catenin is a hallmark feature of Wnt pathway activation [4]. The overexpression of Hypoxia-inducible factor-2α (HIF-2α) upregulates β-catenin levels and promotes its nuclear translocation, enhancing Wnt signaling activity, thereby facilitating the migration of LUAD cells and inducing morphological changes [48]. Moreover, the Wnt pathway determines the fate and self-renewal ability of lung cancer stem cells (CSCs). Preclinical mouse models of LC have indicated that the activation of the Wnt signaling cascade is crucial for maintaining stemness and plasticity, enabling immune evasion, and providing a niche for metastatic potential [49].

The overexpression of Wnt/β-catenin plays an essential role in inducing treatment resistance in LC. Studies have shown that FOXM1 upregulates Wnt/β-catenin activity by directly promoting the transcription of β-catenin in the nucleus, thereby mediating gefitinib resistance and tumor invasiveness [50]. Additionally, Wnt5a plays a role in activating β-catenin-dependent Wnt signaling, affecting radiotherapy efficacy in NSCLC [51]. In addition, the Wnt/β-catenin signaling pathway is a significant potential mechanism for immune evasion and resistance to immune checkpoint inhibitors; mutations in APC and CTNNB1, leading to abnormal activation of the WNT pathway, are key factors inducing immune resistance in LUAD [52].

Biological function of the ncRNA/Wnt/β-catenin axis in LC

Recent studies have identified the driving patterns of epigenetically mediated activation of the Wnt/β-catenin signaling pathway. In particular, ncRNAs (mainly miRNAs, lncRNAs, and circRNAs) are key regulators of the Wnt/β-catenin signaling pathway [53]. A systematic elucidation of the ncRNA/Wnt/β-catenin biological network is expected to provide a new and promising avenue for the diagnosis and treatment of LC.

Regulation of LC cell proliferation, cell metastasis, and invasion

The miRNA/Wnt/β-catenin axis

MiRNAs can regulate the Wnt/β-catenin signaling cascade through either oncogenic or tumor-suppressive effects. Oncogenic miRNAs primarily target APC, a principal element of Wnt/β-catenin signaling. For instance, miR-3607 directly targets APC and inhibits the formation of DC, which activates the Wnt/β-catenin cascade and promotes cancer cell proliferation [54]. Similarly, miR-20b directly targets and negatively regulates APC expression, which activates the Wnt signaling pathway and induces the transcription of miR-20b, creating a positive feedback loop that promotes the proliferation, metastasis, and invasion of NSCLC cells [55]. Exosome-mediated intercellular communication plays important role in LC cell proliferation and metastasis. Xia et al. [56] found that miR-1260b is delivered to surrounding tumor cells via exosomes, subsequently downregulating the expression of the Wnt/β-catenin antagonists secreted frizzled-related protein 1 (sFRP1) and SMAD family member 4 (Smad4), activating the Wnt/β-catenin signaling pathway, and promoting the invasion and metastasis of LUAD. In addition, miR-19b-3p [57], miR-4326 [58], and miR-1254 [59] are upregulated in LC and are significantly associated with increased tumor cell proliferation, metastasis, and invasiveness.

In contrast, some miRNAs act as tumor suppressors by targeting key components and regulators of the Wnt/β-catenin signaling. Wnt is a family of secreted proteins consisting of 19 Wnt signaling ligands [60]. Wnt1 is targeted by miR-148a, which inhibits NSCLC cell proliferation and metastasis [61]. The tumor suppressor miR-1253 directly targets WNT5A (long isoform), thereby reducing WNT5A mRNA levels and obstructing Wnt signaling [62]. FZD proteins are a class of seven-transmembrane receptors that belong to a specialized subfamily of G protein-coupled receptors (GPCRs). miR-203 targets and negatively regulates the expression of FZD2, thereby inhibiting the activation of the canonical Wnt pathway [63]. SRY-box transcription factor 9 (SOX9) is a member of the Sox gene family that regulates growth and development. MiR-185 inhibits the expression of SOX9 and downregulates β-catenin protein levels [64]. Furthermore, Fan et al. [65] demonstrated that the tumor suppressor miR-384 inhibits Wnt signaling by downregulating the expression of the upstream regulator Astrocyte elevated gene-1 (AEG-1). The specific mechanism may be related to the inhibition of AEG-1-mediated phosphorylation of GSK-3β.

The lncRNA/Wnt/β-catenin axis

Recent studies have identified that lncRNAs regulate the Wnt/β-catenin signaling pathway in NSCLC through a competing endogenous RNA (ceRNA) mechanism. For example, the oncogenic lncRNA PVT158 upregulates SOX9 by competitively binding to miR-361-3p, promoting the stability and nuclear translocation of β-catenin to activate the Wnt signaling pathway [66]. NSCLC cells can transport extracellular vesicles (EVs) containing the oncogenic factor AL139294.1 to recipient cells, activating the Wnt/β-catenin pathway through the miR-204-5p/BRD axis, which promotes cell proliferation, migration, and invasion [67]. Conversely, LINC00326, a tumor suppressor, downregulates miR-657 levels to promote dickkopf WNT signaling pathway inhibitor 2 (DKK2) expression in tumor cells. DKK2 acts as a negative regulator of Wnt signaling, thereby blocking the Wnt/β-catenin pathway and inhibiting NSCLC progression [68]. In addition, lncRNA XIST [69], LINC00326 [68], and lncRNA-SNHG7 [70] also function as miRNA sponges to influence the Wnt/β-catenin signaling pathway.

Furthermore, some lncRNAs can promote the activation of Wnt/β-catenin signaling cascades through non-ceRNA mechanisms. Studies indicate that LINC00673-v4 acts as a scaffold protein to enhance the interaction between the DEAD-box helicase DDX3 (DDX3) and casein kinase 1ε (CK1ε), upregulating DVL phosphorylation levels and activating the Wnt/β-catenin signaling pathway [71]. Overexpression of LINC00222 directly reduces the phosphorylation level of GSK3β at the Ser9

site, downregulating Wnt signaling pathway transmission and inhibiting the proliferation, migration, and invasion of LUAD cells [72]. Chang et al. [73] demonstrated that lncRNA ITGB1-DT competitively binds to the epigenetic regulator histone lysine N-methyltransferase EZH2 (EZH2), promoting integrin-β1 (ITGB1) expression and upregulating nuclear β-catenin levels to activate the downstream Wnt pathway. This leads to MYC transcription, which reactivates the lncRNA ITGB1-DT, forming a positive feedback loop that promotes LUAD progression [73]. LncRNA UPLA1 [74], lncRNA AK126698 [75], and LINC00467 [76] also influence Wnt/β-catenin signaling through non-ceRNA mechanisms.

The circRNA/Wnt/β-catenin axis

CircRNAs act as miRNA sponges to regulate signaling pathways, including the Wnt/β-catenin pathway. circ_0018414 acts as a sponge for miR-6807-3p, upregulating DKK1 expression and promoting malignant characteristics in LUAD [77]. Similarly, circ_0006427 targets and negatively regulates miR-6783-3p, promoting DKK1 expression and activating Wnt/β-catenin signaling [78]. Zhao et al. [79] showed that circVAPA silences miR-876-5p, leading to the upregulation of WNT5A and activation of Wnt/β-catenin signaling. Additionally, circ_0001946 [80], circ-PGC [81], circ_0017109 [82], circ-SOX4 [83], and circIGF1R [84] regulate NSCLC cell proliferation and invasion through the miRNA/Wnt/β-catenin axis.

Alternatively, circRNAs are involved in the RNA binding protein (RBP)-mediated activation of the Wnt/β-catenin signaling pathway. For example, circCDR1as is overexpressed in PM(2.5)-induced cancer cells and is positively correlated with malignant features in LC. It specifically binds to serine splicing factor 1 (SRSF1), inhibiting PARK2-mediated ubiquitin degradation of SRSF1, thereby activating the downstream Wnt/β-catenin signaling pathway [85] (Fig. 2; Table 1).

Maintenance/inhibition of tumor stem cell self-renewal and stemness

The miRNA/Wnt/β-catenin axis

Most miRNAs act as oncogenic factors by directly targeting key components or regulatory factors of the Wnt pathway, thereby modulating the classical Wnt signaling pathway to maintain LC stem cell-like traits. For example, miR-1275 directly targets multiple Wnt/β-catenin negative regulators such as DKK3, secreted frizzled-related

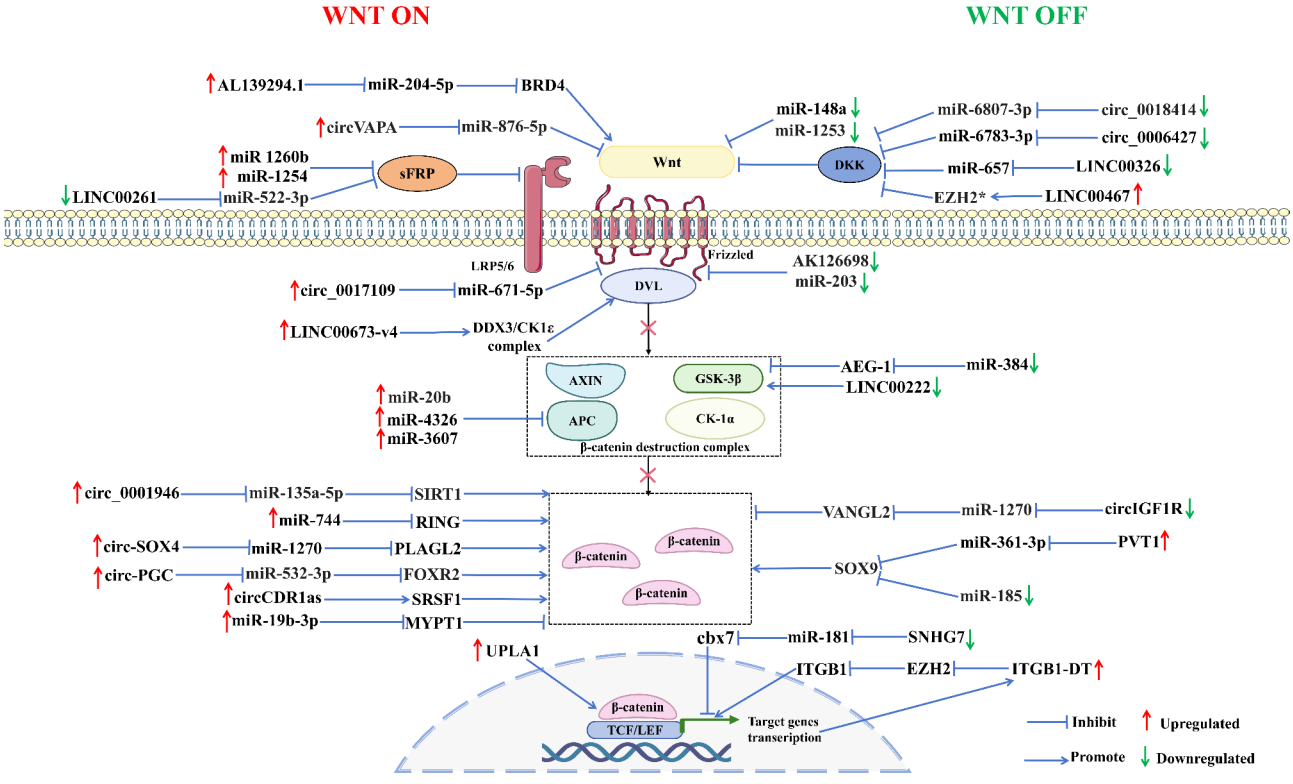

Fig. 2 Wnt/β-catenin-related ncRNAs that regulate tumour cell proliferation, metastasis and invasion. AEG-1: Astrocyte elevated gene-1; BRD4: Bromodomain-containing protein 4; cbx7: chromobox 7; CK1ε: Casein kinase 1ε; DDX3: DEAD-box helicase DDX3; DKK: Dickkopf WNT signaling pathway inhibitor; EZH2: Histone lysine N-methyltransferase EZH2; EZH2*: Zeste 2 polycomb repressive complex 2; FOXR2: Forkhead box R2; ITGB1: Integrinβ1; MYPT1: Myosin phosphatase target subunit 1; PLAGL2: pleomorphic adenoma gene like-2; RING: Ring finger protein; SIRT: Sirtuins; sFRP: secreted frizzled-related protein; SOX9: SRY-box transcription factor 9; SRSF1: Serine splicing factor 1; VANGL 2: VANGL planar cell polarity protein 2

Table 1 Wnt-related NcRNAs regulates proliferation, metastasis, and invasion in LC

No.	ncRNAs	Cell lines used	mechanism of action	Regulation	Oncogene/ suppressor	Biological function	Ref
1	miR-20b	human LUAD cell lines (PC-9, H1975 and A549), a NSCLC cell line (H1299) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of APC expression.	Upregulated	Oncogene	Promote NSCLC cell proliferation, migration, and invasion	[55]
2	miR-19b-3p	Human NSCLC cell lines (A549, NCI-H460 and NCI-H2106) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of MYPT1 blocks the Wnt/β-catenin signaling cascade.	Upregulated	Oncogene	Inhibit NSCLC cell survival, migration, and invasion	[57]
3	miR-3607	Human lung cancer cell lines (NCI-H1650, 95D, A549, NCI-H460, NCI-H358, NCI-H1975 and NCI-H1299) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of APC expression	Upregulated	Oncogene	Promote LC cell proliferation	[54]
4	miR 1260b	Human lung cancer cell lines (A549 and H1299)	Negative regulation of sFRP1 and Smad4 expression.	Upregulated	Oncogene	Promote LUAD cell invasion and metastasis	[56]
5	miR-4326	Human lung cancer cell lines (95D, NCI-H1299, NCI-H460, NCI-H1650, NCI-H358, NCI-H1975, and A549) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of APC2 expression.	Upregulated	Oncogene	Promote LC cell proliferation	[58]
6	miR-1254	Human lung cancer cell lines (A549, NCI-H1975, NCI-H460, 95D, NCI-H1650, A549, NCI-H358 and NCI-H1299) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of SFRP1 expression.	Upregulated	Oncogene	Promote LC cell proliferation	[59]
7	miR-1253	Human NSCLC cell lines (A549, NCI-H1299, NCI-H157, ANIP-973 and GLC-82)	Negative regulation of WNT5A (long isoform) expression.	Downregulated	suppressor	Inhibit NSCLC cell proliferation, migration, and invasion	[62]
8	miR-384	Human NSCLC cell lines (H1299, H1650, H1975, and A549) and human normal lung epithelial cell (BEAS-2B)	Downregulation of AEG expression inhibits Wnt signaling.	Downregulated	suppressor	Inhibit NSCLC cell growth and invasion	[65]
9	miR-148a	Human NSCLC cell lines (A549 and H1299)	Negative regulation of Wnt1 expression.	Downregulated	suppressor	Inhibit NSCLC cell migration and invasion	[61]
10	miR-203	Human NSCLC cell line H1299	Negative regulation of FZD2 expression.	Downregulated	suppressor	Inhibit NSCLC cell proliferation and metastasis	[63]
11	miR-185	Human NSCLC cell lines (A549, H1299, H1650, and the SK-MES-1 NSCLC cell line) and human normal lung epithelial cell (BEAS-2B)	Inhibition of SOX9 expression and downregulation of β-catenin and c-Myc protein levels.	Downregulated	suppressor	Inhibit NSCLC cell proliferation and invasion	[64]
12	lncRNA PVT1	Human NSCLC cell lines (H1650, H1975, H460 and A549) and human normal bronchial epithelial cell line (HBE)	Competitive inhibition of miR-361-3p expression upregulates SOX9, activating the Wnt/β-catenin signaling pathway.	Upregulated	Oncogene	Promote NSCLC cell proliferation, migration, and invasion	[66]
13	lncRNA XIST	Human NSCLC cell lines (A549, H1299, H23, H522, H460, H1650 and 95D)	Targeting the miR-744/RING axis activates the Wnt/β-catenin pathway.	Upregulated	Oncogene	Promote NSCLC proliferation, migration, and invasion	[69]
14	lncRNA AL139294.1	Human NSCLC cell lines (LTEP-A2, NCI-H1299) and human normal lung epithelial cell line (Beas-2B)	Targeting the miR-204-5p/BRD4 axis activates the Wnt pathway.	Upregulated	Oncogene	Promote NSCLC cell proliferation, migration, and invasion	[67]

Table 1 (continued)

No.	ncRNAs	Cell lines used	mechanism of action	Regulation	Oncogene/ suppressor	Biological function	Ref
15	LINC00673-v4	Human LUAD cell lines (HCC827, NCI-H1650, A549, NCI-H596, NCI-H1975, NCI-H1299, SK-LU-1, NCI-H358, NCI-H2009, HCC4006, and NCIH2030)	Enhancement of DDX3 and CK1ε interaction promotes Dvl phosphorylation.	Upregulated	Oncogene	Promote LUAD cell invasion, migration, and metastasis	[71]
16	lncRNA UPLA1	Human LUAD cell lines (A549 and H1299)	Specific binding to DSP promotes Wnt/β-catenin signaling.	Upregulated	Oncogene	Promote LUAD cell migration and invasion	[74]
17	lncRNA ITGB1-DT	Human LUAD cell lines (A549, NCI-H1975 and NCI-H1299) and human bronchial epithelial cell line (16HBE)	Specific binding to EZH2 promotes ITGB1 expression and activates the Wnt/β-catenin pathway.	Upregulated	Oncogene	Promote LUAD progression	[73]
18	LINC00467	Human LUAD cell lines (H1299, Calu, SPC-A1, and A549) and normal human lung epithelial cell (BEAS 2B)	Competitive binding of miR-657 promotes DKK2 expression.	Upregulated	Oncogene	Promote LUAD proliferation and migration	[76]
19	LINC00326	Human NSCLC cell lines (A549NCI-H1299, HCC827, NCI-1650 and NCI-H358)	Targeting the miR-135a-5p/SIRT1 axis activates the Wnt/β-catenin pathway.	Downregulated	suppressor	Inhibit NSCLC progression	[68]
20	lncRNA-SNHG7	Human LUAD cell lines (H3255, HCC827, H1650, A549, H1975, PC9)	Targeting the miR-181/cbx7 axis inhibits Wnt/β-catenin pathway activation.	Downregulated	suppressor	Promote LUAD cell proliferation, inhibit apoptosis	[70]
21	LINC00222	Human LUAD cell lines (SPC-A-1 and LTEP-a-2)	Direct activation of GSK3β activity.	Downregulated	suppressor	Promote LUAD cell migration and invasion	[72]
22	lncRNA AK126698	Human NSCLC cell lines (A549, NCI-H520, and H1299) and human normal human bronchial epithelial cell (16HBE)	Negative regulation of Frizzled-8 expression.	Downregulated	suppressor	Inhibit NSCLC cell proliferation and migration, induce apoptosis	[75]
23	circ_0001946	Human LAC cell lines (H1299, A549, Calu3 and SPC-A1) and human normal lung epithelial cell (BEAS-2B)	Epigenetic silencing of DKK1 expression.	Upregulated	Oncogene	Promote LUAD cell proliferation, colony formation, migration, and invasion	[80]
24	circ-SOX4	Human LUAD cell lines (A549, SPC-A1,H1299, PC-9) and human normal lung epithelial cell (BEAS-2B)	Targeting the miR-1270/PLAGL2 axis activates Wnt/β-catenin signaling.	Upregulated	Oncogene	Promote LUAD cell proliferation, invasion, and migration	[83]
25	circ-PGC	Human SCLC cell lines (H460 and PC9) and human normal lung epithelial cell (BEAS-2B)	Targeting the miR-532-3p/FOXR2 axis activates the Wnt/β-catenin pathway.	Upregulated	Oncogene	Promote NSCLC cell migration, invasion, and glycolysis	[81]
26	circVAPA	Human lung cancer cell lines (H1299, H1975, A549 and HCC827) and human normal lung epithelial cell (BEAS-2B)	Targeting miR-876-5p upregulates WNT5A expression.	Upregulated	Oncogene	Promote NSCLC cell proliferation, migration, invasion, and stemness	[79]
27	circCDR1as	Human NSCLC cell lines (A549, H1299 and H460)	Specific binding to SRSF1 inhibits PARK2-mediated SRSF1 ubiquitination, activating the Wnt/β-catenin signaling pathway.	Upregulated	Oncogene	Promote NSCLC cell proliferation, migration, and invasion	[85]

Table 1 (continued)

No.	ncRNAs	Cell lines used	mechanism of action	Regulation	Oncogene/ suppressor	Biological function	Ref
28	circ_0017109	Human NSCLC cell lines (CALU3, CALU6, A549, H1229), human renal epithelial cell line (H293T) and human bronchial epithelial cells (HBE)	Negative regulation of miR-671-5p upregulates FZD4 expression.	Upregulated	Oncogene	Promote NSCLC cell proliferation, migration, invasion, and stemness	[82]
29	circ_0006427	Human LUAD cell lines (H1299, A549, SPC-A1, and Calu3) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of miR-6783-3p promotes DKK1 expression.	Upregulated	Oncogene	Promote LUAD progression	[78]
30	circ_0018414	Human LUAD cell lines (H1299, A549, SPC-A1, and Calu3) and human normal bronchial epithelial cell line (HBE)	Competitive binding of miR-6807-3p upregulates DKK1 expression.	Downregulated	suppressor	Promote LUAD cell proliferation, colony formation, migration, and invasion	[77]
31	circIGF1R	Human NSCLC cell lines (A549, H1299, Calu-1, H1975, H1650) and normal human fibroblast lung cells (MRC-5)	Competitive binding of miR-1270 promotes the expression of downstream VANGL2, inhibiting the Wnt signaling pathway.	Downregulated	suppressor	Inhibit NSCLC cell invasion and migration	[84]

protein 1 (sFRP1), and GSK3β in NSCLC, activating Wnt/β-catenin signaling and enhancing the stemness of LUAD cells [87]. Hypoxia-inducible factor-1α (HIF-1α) is the most important transcriptional regulator in the hypoxic response. The oncogenic factor miR-1275 is upregulated in a HIF-1α-dependent manner, co-activating the Wnt/β-catenin and Notch signaling pathways to enhance the stem cell-like traits of LUAD cells [87]. In addition, upregulated miR-128-3p [88], miR-582-3p [89], and miR-19 [90] maintain the stem cell-like properties of LC cells by targeting and negatively regulating multiple Wnt/β-catenin negative regulators. Catenin beta interacting protein 1 (CTNNBIP1) is a negative regulator of the Wnt signaling pathway [91]. Qi et al. [92] found that overexpressed miR-214 activates Wnt signaling by negatively regulating CTNNBIP1, thereby maintaining the self-renewal and stemness of LUAD tumor stem cells.

Some miRNAs inhibit LC stemness and tumorigenesis by regulating the Wnt/β-catenin signaling pathway. MiR-708-5p downregulates the levels of DNA methyltransferase 3 A (DNMT3A), which subsequently inhibits the methylation of the tumor suppressor gene CDH1 promoter region. This promotes the formation of the CDH1/β-catenin complex, anchors it to the cell membrane, and blocks the nuclear translocation of β-catenin, leading to the inactivation of the Wnt/β-catenin signaling pathway [93]. Additionally, miR-150-5p targets and negatively regulates HMGA2, GSKIP, and β-catenin, subsequently inhibiting the Wnt/β-catenin signaling pathway and mediating the occurrence, recurrence, and metastasis of CSC-induced NSCLC tumors [94]. MiR-17-92 [86] and miR-191 [86] can indirectly regulate components of the Wnt/β-catenin pathway, such as GSK3 and β-catenin, thereby activating the pathway and significantly promoting the activity of cancer stem cells in LC.

The lncRNA/Wnt/β-catenin axis

LncRNAs promote LC stemness and tumorigenesis by acting as molecular sponges that sequester miRNAs, thereby forming the lncRNA/miRNA/Wnt/β-catenin axis. He et al. [95] showed that the oncogenic lncRNA PKMYT1AR81 acts as a ceRNA of miR-485-5p, promoting protein kinase membrane associated tyrosine 1 (PKMYT1) expression. Subsequently, overexpressed PKMYT1 dose-dependently disrupts the formation of the β-catenin/β-TrCP1 complex, inhibiting the ubiquitination of β-catenin and enhancing the self-renewal of CSCs and their ability to generate differentiated cells in NSCLC [95]. Additionally, lncRNA-DANCR has been shown to be abnormally expressed in various primary human cancers [96, 97]. Yu [98] showed that the oncogenic lncRNA-DANCR activates canonical Wnt signaling through the miR-216a/β-catenin axis in NSCLC. Furthermore, lncRNA-DANCR may induce apoptosis and reduce the metastatic potential of LC cells by inhibiting Sox2, which downregulates the expression of Wnt1/2 and c-MYC [98].

The circRNA/Wnt/β-catenin axis

Increasing evidence suggests that the circRNA/Wnt axis plays a key role in regulating the characteristics of LC stem cells. Li et al. [99] showed that circFBXW7 translates into the short peptide circFBXW7-185AA, which induces β-catenin ubiquitination through a post-translational regulatory mechanism, thereby inhibiting canonical Wnt signaling. Xiong et al. [100] showed that

circRACGAP1 promotes the stemness of NSCLC cells by binding to RBPs. Mechanistically, circRACGAP1 recruits the Polypyrimidine Tract Binding Protein 1 (PTBP1) to enhance the stability and expression of the NAD-dependent deacetylase Sirtuin 3 (SIRT3), which subsequently promotes the deacetylation of replication timing regulatory factor 1 (RIF1), activating the Wnt/β-catenin pathway [100] (Fig. 3; Table 2).

Promotion/inhibition of epithelial-mesenchymal transition (EMT) in tumor cells

The miRNA/Wnt/β-catenin axis

Some miRNAs promote EMT in LC cells by directly or indirectly targeting the Wnt/β-catenin signaling pathway. Cen et al. [102] showed that the oncogenic miR-4739 is upregulated in "driver gene-negative" NSCLC. miR-4739 directly targets the Wnt/β-catenin antagonists APC2 and DKK3, activating the Wnt/β-catenin signaling pathway and enhancing the invasion and metastasis of tumor cells. Additionally in NSCLC cells, miR-4739 is encapsulated in exosomes and transferred to surrounding vascular endothelial cells, where it activates the Wnt/β-catenin pathway to induce angiogenesis and further promote distant tumor metastasis [102]. Yang et al. [103] showed that miR-1246 acts as a promoter of NSCLC cell metastasis by targeting the GSK-3β/β-catenin axis; miR-1246 reduces E-cadherin expression while increasing Vimentin and TGF-β expression, thereby promoting the EMT process in LC. Additionally, some miRNAs target Wnt pathway regulatory factors. For example, the oncogenic miR-489-3p mediates the inhibition of β-catenin ubiquitination by ubiquitin specific peptidase 48 (USP48), inducing malignant phenotypes such as growth, migration, and EMT in NSCLC cells [104]. Similarly, the oncogenic miR-103 targets and downregulates the tumor suppressor kruppel like factor 7 (KLF7), activating Wnt/β-catenin signaling to induce EMT [105].

In contrast, some miRNAs act as tumor-suppressors by directly or indirectly targeting the WNT pathway. Studies have confirmed that miR-3127-5p [106] and miR-577 [107] target key Wnt/β-catenin components such as FZD4 and WNT2B respectively, directly inhibiting EMT and the metastasis of NSCLC. Besides, tumor-suppressive miRNAs indirectly regulate Wnt/β-catenin signaling by influencing upstream regulatory factors in the pathway. The tumor-suppressive miR-770 targets and negatively regulates the oncogene jumonji domain-containing 6 (JMJD6), downregulating the expression of WNT2 and β-catenin, which affects EMT-related protein expression and ultimately inhibits the EMT phenotype [108]. Zinc finger e-box-binding homeobox 1 (ZEB1) is a key transcription factor regulating EMT in NSCLC cells. Qu et al. [109] showed that miR-33b inhibits the expression of EMT markers and affects cell growth, migration, and invasion through the ZEB1/WNT/β-catenin axis. Similarly, ZEB2 is targeted by miR-129, which mediates the

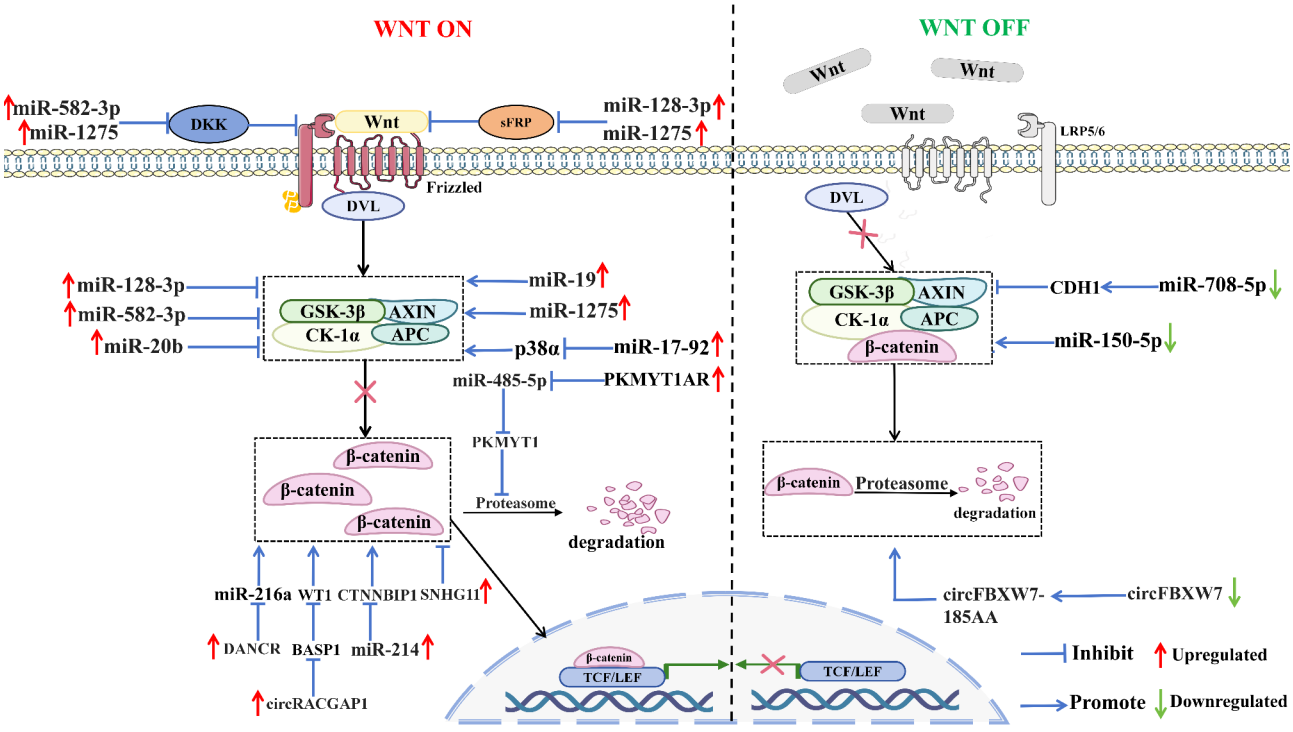

Fig. 3 Wnt/β-catenin-related ncRNAs regulating tumour stem cell properties. BASP1: Brain abundant membrane attached Signal Protein 1; CDH1: Cadherin 1; CTNNBIP1:Catenin beta interacting protein 1; PKMYT1: Protein kinase membrane associated tyrosine 1; WT1:Wilms' tumor protein

Table 2 Wnt-related NcRNAs maintenance/inhibition of tumor stem cell self-renewal and stemness in LC

No.	ncRNAs	Cell lines used	mechanism of action	Regulation	Oncogene/ suppressor	Biological function	Ref
1	miR-1275	Human lung cancer cell lines (L78, H460, A549, GLC-82, SPC-A1, PC9, H1299, H1975, and H2228) and human normal lung epithelial cell (EBAS-2B)	Negative regulation of DKK3, SFRP1, and GSK3β expression through HIF-1α binding.	Upregulated	Oncogene	Maintain CSC properties	[87]
2	miR-128-3p	Human NSCLC cell lines (A549, Calu-3, SK-MES-1, PAa, NCI-H292, NCI-H520 (H520), NCI-H596, NCI-H1299, NCI-H1650, NCI-H1975, HLAMP and 95D) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of Axin1, SFRP2, and WIF1 expression.	Upregulated	Oncogene	Maintain CSC properties, EMT, and induce drug resistance in NSCLC cells	[88]
3	miR-582-3p	Human lung cancer cell lines (A549, 95D, SK-MES-1, NCI-H460, NCI-H358, NCI-H1650, NCI-H1299, NCI-H1703 and NCI-H1975) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of AXIN2, DKK3, and SFRP1 expression.	Upregulated	Oncogene	Maintain CSC properties, promote tumorigenesis, chemotherapy resistance, and recurrence	[89]
4	miR-214	Human lung cancer cell lines (A549 and NCI-H1650)	Negative regulation of CTNNBIP1 promotes β-catenin nuclear accumulation.	Upregulated	Oncogene	Maintain CSC properties	[92]
5	miR-17-92	$Lgr6^+$ human lung stem cells	Negative regulation of p38α inactivates GSK3.	Upregulated	Oncogene	Maintain CSC self-renewal	[101]
6	miR-19	Human lung cancer cell lines (A549 and H1299)	Negative regulation of GSK3β expression.	Upregulated	Oncogene	Inhibit CSC activity	[90]
7	miR-191	Human bronchial epithelial cells malignantly transformed by arsenite	Negative regulation of BASP1 increases WT1 expression.	Upregulated	Oncogene	Promote EMT and CSC-like traits	[86]
8	miR-708-5p	Cell lines A549 and Calu-3 and cell line 95D	Negative regulation of DNMT3A expression, thereby facilitating the formation of the CDH1/β-catenin complex and subsequently blocking the nuclear translocation of β-catenin.	Downregulated	suppressor	Inhibit CSC properties	[93]
9	miR-150-5p	Human NSCLC cell lines (A549, PC-9, and H1299)	Negative regulation of HMGA2, GSKIP, and β-catenin expression.	Downregulated	suppressor	Inhibit CSC properties	[94]
10	lncRNA PKMYT1AR	Human lung cancer cell lines (A549, H1299, H1975, H838, H1650 and SPC-A1) and human normal lung epithelial cell (BEAS-2B)	Competitive binding of miR-485-5p downregulates PKMYT1 expression, preventing the formation of the β-catenin/β-TrCP1 complex, and inhibiting the ubiquitination of β-catenin protein.	Upregulated	Oncogene	Maintain CSC properties	[95]
11	lncRNA-DANCR	Human LUAD cell lines (A549, H1975, H1755, H1944, H2087, and H358) and NSCLC large cell carcinoma cell lines (H661 and H1299)	Competitive binding of miR-216a inhibits β-catenin activity and expression.	Upregulated	Oncogene	Promote CSC self-renewal	[98]
12	circRACGAP1	Human NSCLC cell lines (A549, H1299, H1975, H460, and PC-9) and human bronchial epithelial cell line 16HBE	Recruitment of PTBP1 promotes SIRT3-mediated RIF1 deacetylation, activating the Wnt/β-catenin pathway.	Upregulated	Oncogene	Maintain CSC stemness and metastasis	[100]
13	circFBXW7	Osimertinib resistant H1975OR cells and HCC827OR cells	Translation of a short peptide from circFBXW7-185AA induces β-catenin ubiquitination via post-translational regulatory mechanisms.	Downregulated	suppressor	Inhibit CSC properties, reverse osimertinib resistance	[99]

suppression of the Wnt/β-catenin pathway in NSCLC [110].

The lncRNA/Wnt/β-catenin axis

Most lncRNAs regulate the Wnt/β-catenin pathway via ceRNA mechanisms. Twist1 is a crucial transcription factor mediating the progression of EMT and tumor metastasis [111]. The oncogenic lncRNA JPX accelerates the malignant progression of LC through the miRNA-33a-5p/Twist1/Wnt/β-catenin signaling axis [112]. The oncogenic factor LINC01006 promotes EMT and invasive phenotypes in LUAD through the miR-129-2-3p/CTNNB1/Wnt/β-catenin axis [113]. Additionally, the tumor suppressor LINC01089 negatively regulates SFRP1 expression by sponging miR-27a, disrupting the interaction between Wnt ligands and FZD, thereby inhibiting the EMT process mediated by the Wnt/β-catenin signaling pathway [114]. Liu et al. [115] found that the oncogenic factor lncRNA SNHG11 not only activates the Wnt/β-catenin pathway through the miR-4436a/CTNNB1 ceRNA axis but also binds directly to β-catenin, promoting its nuclear translocation. Activation of the canonical Wnt pathway by SNHG11 enhances cancer cell proliferation, migration, invasion, and EMT. In addition, lncRNA FEZF1-AS1 directly downregulates the expression of Axin1, promoting the nuclear accumulation of β-catenin [116].

The circRNA/Wnt/β-catenin axis

Gao et al. [117] demonstrated that the tumor suppressor hsa_circ_0007059 inhibits the expression of Wnt3a and β-catenin through sponging miR-378. This mechanism subsequently promotes the expression of E-cadherin and downregulates Vimentin, Twist1, and ZEB1, thereby suppressing EMT in NSCLC cells [117]. Another study revealed that the oncogenic factor circ_0067934 acts as a sponge for miR-1182 and promotes the activation of Wnt/β-catenin signaling mediated by kruppel-like factor 8 (KLF8) [118]. In addition to oncogenic circRNAs, some tumor suppressor circRNAs also regulate Wnt/β-catenin signaling through a ceRNA mechanism. For example, circ-GSK3B regulates GSK3B mRNA expression in LUAD by acting as a ceRNA sponge for miR-3681-3p and miR-3909, thereby promoting GSK3B expression. Additionally, circ-GSK3B can bind to the N-terminal FK1 domain of FK506 binding protein 51 (FKBP51), weakening the interaction between FKBP51 and GSK-3β, which inhibits the phosphorylation of GSK-3β at S9, thereby inactivating Wnt/β-catenin signaling and suppressing EMT in LUAD cells [119] (Fig. 4; Table 3).

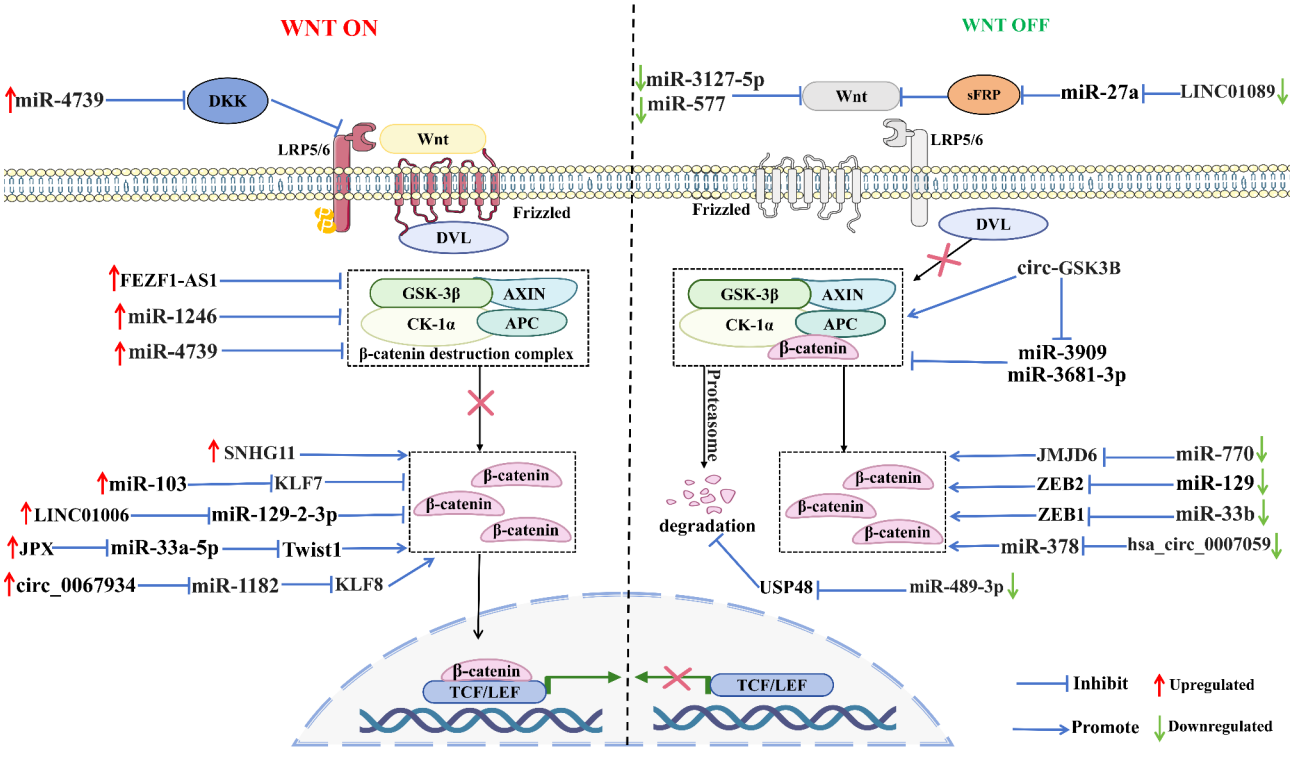

Fig. 4 Wnt/β-catenin-related ncRNAs regulating EMT in lung cancer. FKBP51: FK506 binding protein 51; KLF7: Kruppel like factor 7; JMJD6: Jumonji domain-containing 6; KLF8: Kruppel like factor 7; USP48: Ubiquitin specific peptidase 48; ZEB1: Zinc finger E-box-binding homeobox 1; ZEB2: Zinc finger E-box-binding homeobox 2

Table 3 Wnt-related NcRNAs promotion/inhibition of EMT in tumor cells

No.	ncRNAs	Cell lines used	mechanism of action	Regulation	Oncogene/ suppressor	Biological function	Ref
1	miR-4739	"Driver gene-negative" NSCLC cell lines (H2085 and H2126) and HUVECs	Negative regulation of APC2 and DKK3 expression.	Upregulated	Oncogene	Promote EMT in NSCLC cells	[102]
2	miR-489-3p	Human NSCLC cell lines (H1299, A549, MIRC5 and SK-LU-1) and human normal lung epithelial cell line (BEAS-2B)	Negative regulation of USP48 to inhibit β-catenin ubiquitination.	Upregulated	Oncogene	Inhibit EMT, proliferation, and migration in NSCLC cells	[104]
3	miR-103	Human NSCLC cell lines (A549, H1299 and H460) and human normal bronchial epithelial cell line (16HBE)	Negative regulation of KLF7 activates the Wnt/β-catenin signaling pathway.	Upregulated	Oncogene	Promote EMT, migration, and invasion in NSCLC cells	[105]
4	miR-1246	Human NSCLC cell line A549	Negative regulation of GSK-3β but increases β-catenin levels.	Upregulated	Oncogene	Promote EMT in LC cells	[103]
5	miR-770	Human NSCLC cell lines (H522, H650, H1155, H1299 and A549) and human normal bronchial epithelial cells (HBECs)	Negative regulation of JMJD6 inhibits the Wnt/β-catenin pathway.	Downregulated	suppressor	Inhibit NSCLC EMT	[108]
6	miR-129	Human NSCLC cells (NCI-H460, NCI-H1299, and A549) and human normal lung epithelial cell (BEAS-2B)	Negative regulation of ZEB2 inhibits Wnt/β-catenin signaling.	Downregulated	suppressor	Inhibit EMT in NSCLC	[110]
7	miR-33b	Human lung cancer cell lines (HBE, A549, h1299, SPC-α-1, PC-9, LIEP-α-2 and HTB182)	Negative regulation of ZEB1 expression inhibits Wnt/β-catenin signaling.	Downregulated	suppressor	Inhibit LUAD growth and EMT	[109]
8	miR-3127-5p	Human lung cancer cell lines (A549 and H1299)	Negative regulation of FZD4 expression.	Downregulated	suppressor	Inhibit NSCLC EMT, migration, invasion, and adhesion	[106]
9	miR-577	Human NSCLC cell lines (H650, A549, H522, H1299 and H1155) and human normal bronchial epithelial cells (HBECs)	Negative regulation of WNT2B expression levels.	Downregulated	suppressor	Inhibit NSCLC EMT, migration, and invasion	[120]
10	lncRNA JPX	Human LUAD cell lines (SPC-A-1, LTEP-a-2, A549, NCI-H1299) and human normal lung epithelial cell (BEAS-2B)	Targeting miR-33a-5p/Twist1 activates the Wnt/β-catenin signaling pathway.	Upregulated	Oncogene	Promote EMT in LC cells	[112]
11	lncRNA FEZF1-AS1	Human NSCLC cell lines (A549, SPC-A1, H1299, H1975, PC9) and human normal bronchial epithelial cell line (16HBE)	56. Downregulation of Axin1 expression promotes β-catenin nuclear accumulation.	Upregulated	Oncogene	Inhibit NSCLC EMT, reduce proliferation and invasion	[116]
12	lncRNA SNHG11	human lung cancer cell lines (A549, H1299, H460, and SPCA1) and human normal bronchial epithelial cell line (16HBE)	(1) Sponge miR-4436a promotes CTNNB1 expression and activates the Wnt/β-catenin pathway; (2) Direct binding to β-catenin activates the canonical Wnt pathway.	Upregulated	Oncogene	Promote LUAD progression	[115]
13	LINC01006	Human LUAD cell lines (PC9, H1650, H1975, and A549) and human normal lung epithelial cell (BEAS-2B)	Competitive binding of miR-129-2-3p promotes CTNNB1 expression and activates the Wnt/β-catenin pathway.	Upregulated	Oncogene	Promote LUAD cell proliferation, migration, and EMT	[113]
14	LINC01089	Human NSCLC cell lines (A549, H1299, H460, PC9) and human normal lung epithelial cells (EBAS-2B)	Targeting miR-27a/SFRP1 expression inhibits Wnt/β-catenin signaling.	Downregulated	suppressor	Inhibit NSCLC EMT	[114]

Table 3 (continued)

No.	ncRNAs	Cell lines used	mechanism of action	Regulation	Oncogene/ suppressor	Biological function	Ref
15	circ_0067934	Human NSCLC cell lines (H358 and H23) and human normal bronchial epithelial cell line (16HBE)	Targeting miR-1182/KLF8 activates the Wnt/β-catenin signaling pathway.	Upregulated	Oncogene	Promote EMT in NSCLC and induce apoptosis	[118]
16	circ-GSK3B	Human normal lung epithelial cells (BEAS-2B) and human LUAD cell lines (PC9, H2073, H-1975, A549)	(1) Competitive binding of miR-3681-3p and miR-3909 promotes GSK3B expression; (2) Circ-GSK3B binding FKBP51 inhibits FKBP51-mediated phosphorylation of GSK-3β at Ser9.	Downregulated	suppressor	Inhibit LUAD EMT, tumor progression	[119]
17	hsa_circ_0007059	Human lung cancer cell lines (A549 and H1975)	Competitive binding of miR-378 inactivates the Wnt/β-catenin pathway.	Downregulated	suppressor	Inhibit EMT in LC cells	[117]

Clinical applications of Wnt axis-associated NcRNAs in LC

Early detection markers for LC

LDCT screening's overdiagnosis and false-positive rates hinder early LC diagnosis [121]. Therefore, there is an urgent need for new diagnostic biomarkers, with liquid biopsy ncRNA detection emerging as a promising solution [122]. Recent studies have demonstrated that Wnt pathway-related ncRNAs are potential early liquid biopsy biomarkers for LC. Pan et al. [123] evaluated the characteristics of miR-33a-5p and miR-128-3p in the peripheral whole blood of patients with LC and found that miR-33a-5p (AUC = 0.870) and miR-128-3p (AUC = 0.9278) both demonstrate advantages as tumor markers for the early diagnosis of LC. Their sensitivity and specificity are significantly superior to those of traditional tumor markers, and the combination of these two biomarkers enhances the diagnostic accuracy for cancer (AUC = 0.951). Given their high stability in plasma, miR-33a-5p and miR-128-3p hold potential as novel diagnostic and prognostic biomarkers for the early detection of LC [123]. Notably, plasma exosomal ncRNAs have significant potential as innovative biomarkers for liquid biopsy [124]. Xia et al. [56] found that plasma exosomal miR-1260b serves as a diagnostic biomarker for LUAD with a sensitivity of 72% and specificity of 86%, yielding an AUC of 0.845. This indicates its potential as a specific marker for LUAD diagnosis [56]. Additionally, Zhang et al. [125] found that miR-20b-5p in plasma EVs is significantly associated with early stage NSCLC (stages 0 and I) (AUC = 0.810). Furthermore, using a panel of miR-20b-5p and miR-3187-5p improves the AUC to 0.838, indicating enhanced diagnostic potential [125]. Overall, the current evidence suggests that Wnt axis-related ncRNAs show promising results as diagnostic indicators of NSCLC, particularly highlighting that ncRNA combination panels demonstrate accurate predictive performance for detecting early stage NSCLC.

Markers for recognizing pathological types of LC

Traditional tissue biopsy is often regarded as the gold standard for pathological diagnosis; however, it is invasive and may not fully capture the diverse characteristics and evolving nature of the tumor [126]. NcRNA-based liquid biopsy has potential clinical significance for identifying the pathological types of LC, particularly because miRNAs have been shown to be effective biomarkers for the classification of NSCLC tissue types [127, 128]. Liu et al. [93] studied the expression of miR-708-5p in 148 paired NSCLC samples and its relationship with clinicopathological features. Their findings indicated that miR-708-5p exhibits high sensitivity and specificity for LC histological diagnosis (AUC = 0.881), making it a significant biomarker for differentiating lung squamous cell carcinoma (LUSC) from LUAD [93]. Additionally, Baran et al. [129] demonstrated that the expression levels of miR-150 and LINC00673 are significantly different across the histopathological types of NSCLC. Compared with patients with LUSC, a significant decrease in miR-150 and increase in LINC00673 expression levels were observed in the serum EVs of patients with LUAD. Evaluation of the RQ values of both biomarkers in serum EVs suggests that the combination of miR-150 and LINC00673 could serve as a non-invasive biomarker for distinguishing between LUAD and LUSC [129].

Clinical staging markers for LC

The clinical staging of tumors helps assess the extent of disease progression, determine the most effective treatment options, and evaluate treatment outcomes [130]. The highly expressed lncRNA-DANCR positively correlates with larger tumor size, advanced TNM staging, and lymph node metastasis [131]. Multiple studies have found that the lncRNAs XIST59, FEZF1-AS1102, and AC026356.1122 are associated with lymph node metastasis, poor differentiation grade, and advanced TNM stage [132]. These three lncRNAs may serve as potential

biomarkers for the clinical staging of NSCLC. LINC00222 is negatively correlated with tumor size, tumor stage, and lymphatic metastasis, while also indicating a high recurrence rate and shorter overall survival (OS) [72]. Additionally, Ma et al. [67] indicated that lncRNA AL139294.1 is significantly upregulated in serum EVs of patients with NSCLC. Furthermore, lncRNA AL139294.1 and its ceRNA miR-204-5p in EVs are closely associated with advanced pathological staging, lymph node metastasis, and distant metastasis in NSCLC [67].

Biomarkers for prognostic analysis of LC

ncRNAs are closely associated with patient prognostic features, and differentially expressed ncRNAs can serve as independent prognostic factors for LC. Prognostic models based on these ncRNAs will aid in treatment decision-making for LC [133, 134]. Clinical studies have shown that miR-1275 levels are significantly associated with tumor differentiation, distant metastasis, and TNM clinical staging, and patients with high miR-1275 levels have a higher tumor recurrence rate. Thus, miR-1275 can serve as an independent predictor of OS in these patients [87]. Jiang et al. [87] found that a predictive model combining miR-1275 with β-catenin and Notch intracellular domain (NICD) demonstrated an optimal predictive capability for metastasis, with an AUC of 0.879. Fang et al. [89] analyzed miRNAs associated with NSCLC recurrence and patient survival and identified miR-582 as the only miRNA significantly correlated with both recurrence-free survival (RFS) and OS. Therefore, miR-582 can serve as an independent indicator of prognostic assessment and early recurrence in NSCLC patients [89].

Moreover, the expression levels of miR-1253 [135] and miR-489-3p [104] are significantly downregulated in NSCLC tissues and are closely associated with advanced tumor stage, poor OS, and high recurrence rates. These miRNAs are potential biomarkers of an unfavorable prognosis in patients with NSCLC. Võsa et al. [136] analyzed the expression profiles of 858 miRNAs in NSCLC samples (stage I and II) and adjacent non-tumor tissues, revealing that miR-374a can serve as an early-stage risk stratification tool for NSCLC progression and a clinically useful independent prognostic indicator. Notably, the blood and tissues of patients with LC exhibit unique exosomal ncRNA features, which show promise as potential prognostic biomarkers for LC [137, 138]. For example, Cen et al. [102] found that miR-4739 in EVs can serve as an independent prognostic factor for OS in patients with LC. CircRNAs are exceptionally stable in bodily fluids, making them potential non-invasive biomarkers for cancer [139]. Yao et al. [80] indicated that circ_0001946 has a stronger prognostic impact in patients with stage III NSCLC and serves as an indicator of sensitivity to adjuvant chemotherapy post-surgery.

Potential therapeutic targets for LC

Current research confirms the key role of ncRNAs in the development of LC, particularly in acquired drug resistance, where ncRNAs are extensively involved in Wnt pathway-mediated mechanisms of resistance in LC cells [140]. Targeting ncRNAs may be an effective strategy for the development of new therapies to overcome treatment resistance in LC [141]. First, ncRNAs play a crucial role in EGFR-TKI resistance in NSCLC. Studies have shown that circ-FBXW7 inhibits tumor stem cell growth and self-renewal by blocking the Wnt signaling pathway, making it an effective strategy to enhance the efficacy of osimertinib and reverse resistance [99]. Additionally, lncRNA NEAT1 enhances the pro-apoptotic and cytotoxic effects of anlotinib. Combining anlotinib with lncRNA NEAT1 knockdown may offer a new therapeutic strategy for patients with NSCLC [142]. Wang et al. [136] indicated that miR-374a and miR-548b jointly regulate the cell cycle, apoptosis, and migration and invasion of gefitinib-resistant NSCLC cells. Both miR-374a and miR-548b may be important targets for overcoming acquired resistance to EGFR-TKIs in the treatment of NSCLC.

Additionally, Wnt pathway-related ncRNAs are involved in chemotherapy resistance in LC. Research has shown that overexpressed lncRNA NEAT1 mediates the Wnt signaling pathway, enhancing the stemness of A549 cells, and further inducing cisplatin resistance in tumor cells. Therefore, lncRNA NEAT1 may serve as a target for CSCs in NSCLC chemotherapy resistance [143]. LncRNA SNHG1 promotes the invasiveness of cell lines and cisplatin (CDDP) resistance through the miR-140-5p/Wnt/β-catenin axis. In comparison, SNHG1 knockdown improves CDDP resistance in NSCLC cells. Additionally, lncRNA RPPH1 [144] and miR-130b [145] regulate Wnt/β-catenin-mediated chemotherapy resistance in LC. Given the crucial role of ncRNAs in chemotherapy resistance, targeting specific ncRNAs may offer a new strategy to overcome resistance in LC. Notably, existing preclinical studies have shown that antisense oligonucleotide (ASO) therapies effectively inhibit tumor growth in both in vitro and in vivo models of LC [146, 147]. He et al. [95] demonstrated that targeting the PKMYT1AR/miR-485-5p/PKMYT1 axis is an effective therapeutic strategy for LC. ASOs against PKMYT1AR can significantly inhibit the proliferation, migration, and self-renewal capacity of CSCs [95] (Table 4).

Opportunities, challenges, and future directions of NcRNAs in the clinical translation of LC

Mechanistic complexity of NcRNAs in LC pathogenesis: bridging knowledge gaps

Current isolated mechanistic studies on single regulatory axes remain insufficient to fully elucidate the pan-regulatory landscape of ncRNA-mediated Wnt signaling

Table 4 Clinical applications of Wnt-related NcRNAs NcRNAs in LC

NO.	Clinical Application	ncRNAs	Material Source	Function	Ref
1	LUAD clinical staging markers, independent prognostic markers	miR-1275	13 pairs of LUAD and adjacent non-tumor tissues, along with 558 LUAD samples from three independent cohorts (SYSUFH, SYSUCC, CHWH)	High differentiation and advanced clinical stage ($P<0.001$)	[87]
2	NSCLC diagnostic markers, clinical staging markers, independent prognostic markers	miR-128-3p	153 NSCLC tissue specimens and 234 NSCLC specimens from patients who received multiple cycles of cisplatin (CDDP)-based first-line chemotherapy	Advanced clinical stage ($P<0.001$), poor OS and PFS ($P<0.001$), and differentiation of NSCLC histological types	[88]
3	LC independent prognostic markers	miR-582-3p	150 NSCLC tumor specimens from an external lung cancer database	Poor RFS and OS ($P<0.01$)	[89]
4	LUAD clinical staging markers, prognostic biomarkers	miR-214	8 LUAD tumor samples and 90 stage IIIA LUAD patient samples;	Advanced clinical stage; poor OS and high recurrence rate	[92]
5	LC pathological type markers, prognostic biomarkers	miR-708-5p	Lung cancer external databases (TCGA cohort and FDPQG cohort)	Long OS and RFS ($P=0.003$); differentiation of NSCLC histological types (AUC = 0.859, $P<0.001$)	[93]
6	NSCLC prognostic biomarkers	miR-150-5p	111 NSCLC tissue samples (47 with low miR-150 expression; 64 with high miR-150 expression)	Longer TTP, PFS, and OS ($P=0.04$)	[94]
7	NSCLC clinical staging markers, diagnostic biomarkers	miR-20b	276 NSCLC patients (104 with stage 0-I; 172 with stages II-IV) and 282 healthy control serum samples	early-stage NSCLC (Stages 0 and I) ($P<0.0001$, AUC = 0.81).	[125]
8	NSCLC clinical staging and prognostic markers	miR-19b-3p	68 paired NSCLC tumor tissues and adjacent normal tissues	Advanced clinical TNM stage ($P=0.024$) and shorter OS ($P=0.0394$)	[57]
9	NSCLC gefitinib resistance markers and clinical staging biomarkers	miR-374a	40 NSCLC tissue samples	Shorter DFS ($P=0.0342$) and gefitinib resistance maker ($P<0.05$)	[148]
10		miR-548b		Longer DFS ($P=0.0342$) and gefitinib resistance maker ($P<0.05$)	
11	NSCLC clinical staging markers	miR-3607	39 NSCLC tissue samples	Advanced clinical stage	[54]
12	LUAD diagnostic biomarkers	miR 1260b	50 LUAD patient tissue and plasma samples	Early diagnosis of LUAD (AUC = 0.845, sensitivity 72%, specificity 86%)	[56]
13	NSCLC clinical staging markers, prognostic markers	miR-1253	157 pairs of NSCLC tissues and matched non-cancerous lung tissues	Earlier clinical stages in NSCLC ($P=0.001$) and longer OS ($P=0.003$)	[62]
14	NSCLC clinical staging markers, independent prognostic markers	miRNA-148a	165 pairs of NSCLC samples (90 adenocarcinomas and 75 squamous cell carcinomas) and their adjacent normal lung tissues	Longer OS ($P=0.031$)	[61]
15	NSCLC clinical staging markers, independent prognostic markers	miR-4739	160 pairs of primary "driver gene-negative" NSCLC tumor tissues and adjacent non-tumor tissues	Shorter OS ($P<0.001$); advanced clinical stage	[102]
16	NSCLC clinical staging markers, prognostic biomarkers	miR-770	50 pairs of non-small cell lung cancer tissues and adjacent normal tissues	Negative correlation with tumor size ($P=0.002$), pathological grade ($P=0.015$), and lymph node metastasis ($P=0.010$); longer OS ($P<0.05$)	[108]
17	NSCLC prognostic markers	miR-129	51 pairs of NSCLC tissue specimens	Longer OS ($P<0.01$).	[110]
18	NSCLC clinical staging markers, prognostic markers	miR-577	25 NSCLC tissue samples and adjacent normal lung tissues	Advanced TNM stage and lymph node metastasis ($P<0.05$).	[120]
19	NSCLC clinical staging markers, prognostic markers	lncRNA DANCR	32 pairs of NSCLC and adjacent normal lung tissues	Larger tumor size ($P<0.0001$), advanced TNM stage ($P=0.002$), lymph node metastasis ($P=0.012$), and poor OS ($P=0.0024$).	[131]
20	NSCLC diagnostic markers, clinical staging markers, and prognostic biomarkers	lncRNA AL139294.1	111 pre-treatment NSCLC serum samples and 49 serum samples from pneumonia patients	Significant differentiation between healthy samples and NSCLC samples (AUC = 0.915)	[67]
21	NSCLC staging markers, prognostic markers	LINC00673-v4	119 LUAD tissues and adjacent non-tumor tissues from the external lung cancer database	Lymph node metastasis; shorter OS ($P=0.0002$)	[71]

Table 4 (continued)

NO.	Clinical Application	ncRNAs	Material Source	Function	Ref
22	NSCLC diagnostic markers	LINC00673	Serum samples from 30 NSCLC patients and 30 NSCLC tumor samples with matching adjacent non-cancerous tissues	Serum LINC00673 combined with miR-150 can differentiate LUSD and LUAD types ($P=0.03$); early diagnostic marker for NSCLC (AUC = 0.784, sensitivity 80%, specificity 80%)	[129]
23	LUAD clinical staging markers, independent prognostic factors	lncRNA UPLA1	78 pairs of surgically resected LUAD tissues and matching adjacent normal tissues	Larger tumor size ($P<0.01$), advanced TNM stage ($P<0.001$), and shorter OS ($P<0.05$)	[74]
24	LUAD clinical staging markers, prognostic biomarkers	lncRNA ITGB1-DT	64 pairs of LUAD tissues and matching normal lung tissues	Poor OS ($P=0.0334$) and DFS ($P=0.0404$); lymph node metastasis and advanced TNM stage ($P<0.05$)	[73]
25	NSCLC clinical staging markers, prognostic markers	LINC00326	96 NSCLC tumor samples and their adjacent normal tissues	Earlier NSCLC TNM stage ($P=0.0021$), longer OS ($P=0.0057$)	[68]
26	LC prognostic markers	lncRNA-SNHG7	112 pairs of tumor and adjacent non-tumor tissues	Longer DFS and OS ($P=0.035$, $P=0.0071$)	[70]
27	LUAD prognostic markers	LINC00222	76 lung adenocarcinoma tissues and adjacent non-tumor lung tissues	Lower recurrence rate and longer OS and DFS ($P<0.05$)	[72]
28	LC clinical staging markers, prognostic biomarkers	lncRNA JPX	116 primary lung cancer tissues and corresponding adjacent tissues	Larger tumor size ($P=0.0009$), later TNM stage ($P=0.0003$)	[112]
29	LC clinical staging markers, prognostic biomarkers	lncRNA FEZF1-AS1	86 matched NSCLC tumor tissues and adjacent normal tissues	NSCLC lymph node metastasis ($P=0.022$), higher tumor differentiation ($P=0.001$), and advanced TNM stage ($P=0.012$) are positively correlated	[116]
30	LC clinical staging markers, prognostic biomarkers	lncRNA SNHG11	42 pairs of matched lung cancer tissues and adjacent normal tissues	Advanced TNM stage ($P=0.01$) and larger tumor size ($P=0.012$)	[115]
31	NSCLC prognostic biomarkers	LINC01089	60 pairs of non-small cell lung cancer tumor and adjacent normal tissues	Advanced TNM stage ($P=0.035$), lymph node metastasis ($P=0.0307$), and poor differentiation ($P=0.0044$); poor OS ($P=0.0067$)	[114]
32	NSCLC prognostic biomarkers	circRACGAP1	56 pairs of NSCLC tissues and adjacent normal lung tissues, with serum samples	Poor OS ($P=0.015$)	[100]
33	LUAD clinical staging markers, prognostic biomarkers	circ_0001946	72 pairs of LAC patient tumor tissues and adjacent normal tissues	Advanced TNM stage ($P=0.002$), larger tumor size ($P=0.004$), and poor OS ($P=0.002$)	[80]
34	NSCLC prognostic markers	circ-PGC	33 pairs of NSCLC patient tumor tissues and adjacent normal tissues	Poor 5-year OS ($P=0.023$)	[81]
35	NSCLC prognostic biomarkers	circVAPA	45 matched pairs of NSCLC tumor tissues and adjacent normal tissues	Poor OS ($P<0.05$)	[79]
36	NSCLC clinical staging markers, prognostic markers	circ_0017109	50 pairs of NSCLC tissues and matched non-tumor tissues	Larger tumor size ($P=0.047$), lymph node metastasis ($P=0.0308$), and advanced TNM stage ($P=0.0227$); correlated with poor OS ($P=0.009$)	[82]
37	NSCLC clinical staging markers, prognostic biomarkers	circ_0006427	94 pairs of matched LUAD tumor and non-tumor specimens	Advanced TNM stage ($P=0.006$), larger tumor size ($P<0.001$), and lymph node metastasis ($P=0.011$); help distinguish early (Stage I-II) from late-stage (Stage III-IV) disease; poor OS ($P=0.005$)	[78]
38	LUAD prognostic biomarkers	circ_0018414	40 pairs of matched LUAD tissues and non-tumor tissues.	Longer OS ($P=0.001$)	[77]
39	NSCLC staging markers	hsa_circ_0007059	20 pairs of matched lung cancer tissues and adjacent non-tumor tissues	Downregulated ($P<0.001$); earlier clinical stages ($P<0.01$)	[117]

modulation in LC. Emerging evidence indicates that specific ncRNAs can simultaneously target Wnt, Hedgehog, and Notch pathways to drive LC progression, highlighting their capacity to orchestrate crosstalk between multiple signaling cascades [149, 150]. Solely focusing on Wnt signaling may lead to an incomplete understanding of lung carcinogenesis. Thus, establishing a Wnt-associated multi-pathway ceRNA network becomes imperative for deciphering the intricate molecular mechanisms underlying LC. This integrative approach not only elucidates

how ncRNAs coordinate tumorigenesis through multi-pathway regulation but also facilitates the identification of context-dependent therapeutic targets.

Genetic alterations (e.g., activating mutations in oncogenes or inactivating mutations in tumor suppressor genes) often have powerful driver effects, which can mask or modify epigenetic regulation mediated by ncRNAs to some extent, and may even outweigh the effects of ncRNA-mediated epigenetic modifications. For example, aberrant expression and/or mutations of EGFR may also alter the expression of oncogenic miRNAs (e.g., miR-21) in LC [151]. However, although genetic alterations may outweigh the effects of epigenetic modifications, the two do not exist in isolation but interact in complex ways. Emerging evidence indicates that certain dysregulated miRNAs in LC (e.g., miR-141-3p and miR-203) modulate EGFR mutation-driven pathways, thereby contributing to resistance against targeted therapies [152]. Therefore, in-depth analysis of the synergistic and antagonistic mechanisms between genetic and epigenetic regulation will help overcome the limitations of single therapeutic target studies and provide more comprehensive strategies for the precision treatment of LC. Future studies should integrate genome-wide, transcriptomic, and epigenomic data to systematically analyze the interactions between genetic alterations and epigenetic modifications. Additionally, dCas9-mediated epigenetic-editing tools can be used to accurately simulate oncogene mutations or tumor suppressor gene inactivation [153, 154], enabling the study of ncRNA functions in the context of genetic mutations.

ncRNA-based diagnostic biomarkers: from discovery to clinical validation

As of February 2025, a search of the Clinical Trial Registry Platform (https://clinicaltrials.gov/) reveals that a number of ncRNA-based clinical studies have been registered in the field of LC, with research topics focusing on exploring the value of ncRNAs as novel biomarkers in the diagnosis or prognostic assessment of the disease. Non-invasive liquid biopsy based on ncRNAs holds promising potential for early diagnosis, prognostic development, drug resistance monitoring, and improving diagnostic efficiency when combined with classical tumor markers in NSCLC [155, 156]. However, current research faces limitations, including a lack of highly specific and sensitive biomarkers, limited sample sizes, and the vast number of ncRNA targets, which may hinder a full understanding of the feasibility of ncRNAs as diagnostic and therapeutic biomarkers for NSCLC. Notably, some studies on specific miRNAs (e.g., miR-143/miR-145, miR-29) in LC report contradictory findings [157–159], which may be attributed to factors such as variations in sample sizes, heterogeneity of patient populations, and differences in experimental methods. Therefore, conducting large-scale, multi-center studies and utilizing high-sensitivity, high-specificity detection platforms is crucial to further validate the effectiveness of ncRNAs as biomarkers. Furthermore, ncRNA-related databases furnish a comprehensive resource platform for predicting their function and determining their association with disease. By integrating artificial intelligence (AI), these databases can ascertain whether ncRNAs reflect cancer-specific or population-specific outcomes, providing substantial support for clinical translation and future research directions [160, 161].

Therapeutic targeting of NcRNAs: delivery challenges and emerging strategies

While targeted design of RNA-based therapeutics and their delivery systems constitute both a pivotal challenge and a research frontier in current RNA therapy development, this modality undeniably represents a paradigm shift for addressing historically undruggable targets and intractable diseases. Given the demonstrated potential of Wnt-associated ncRNAs in overcoming therapeutic resistance in LC, coupled with the emergence of accessible platforms including antisense RNAs, small interfering RNA (siRNA), ASO, and aptamers, these advances collectively furnish an expansive landscape for the innovation of RNA pharmaceuticals with enhanced mechanistic specificity [162–165]. However, current RNA modulation tools (e.g., RNAi and antisense RNA technology) are plagued by substantial non-specific degradation and imprecise RNA targeting, where off-target effects may aberrantly interfere with critical cellular processes, thereby compromising therapeutic efficacy or inducing adverse effects [166–168]. Notably, recent advancements in enhancing RNA therapy specificity have been achieved through multiple innovative strategies. The implementation of novel chemical modifications (such as locked nucleic acid (LNA) and 2'-O-methyl modifications) has demonstrated remarkable improvements in the thermodynamic stability and binding specificity of siRNA/ASO, effectively minimizing off-target interactions. Moreover, the evolution of CRISPR-Cas systems now enables precise epigenome editing through site-specific genomic alterations, offering unprecedented precision in therapeutic targeting [169, 170]. Pioneering studies have validated that the CRISPR-Cas13 system can achieve circRNA-specific knockdown without perturbing cognate linear mRNA isoforms, exemplifying its potential for selective RNA regulation [171, 172].

Conclusion

An incomplete understanding of the molecular events associated with LC development, challenges in developing highly sensitive and specific early detection methods,

and widespread resistance to LC treatments are significant bottlenecks in effectively overcoming LC. NcRNAs target multiple key components and regulatory factors of the Wnt/β-catenin signaling pathway, participating in the expression of Wnt/β-catenin pathway target genes in LC. NcRNAs regulate cancer cell stemness, proliferation, metastasis, invasion, and treatment resistance. Additionally, Wnt-related ncRNAs serve as effective, multifunctional biomarkers for early diagnosis, prognosis, and monitoring of treatment response in LC, showing promise for personalized medicine. Overall, the key role of ncRNAs in regulating the Wnt/β-catenin signaling pathway is promising and should be a focus of future research to overcome challenges in the understanding, diagnosis, and treatment of LC.

Abbreviations

ASO	Antisense Oligonucleotide
AUC	Area under the curve
CDDP	Cisplatin
EGFR-TKI	Epidermal growth factor receptor-Tyrosine kinase inhibitor
EVs	Extracellular vesicles
HIF-1α	Hypoxia-inducible factor-1α
LC	Lung Cancer
LDCT	Low-dosecomputedtomography
LNA	Locked Nucleic Acid
LUAD	Lung adenocarcinoma
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
RFS	Free survival
RQ	Root mean square deviation
siRNA	small interfering RNA
TCF/LEF	T cell factor/lymphoid enhancer factor
UTR	Untranslated Regions
β-TrCP	β-transducin repeat-containing protein

Supplementary Information

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Supplementary Material 1

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Author contributions
Conceptualization: Y.Z., J.W-H., and Q.M.Writing—original draft preparation: Y.Z., C.X-H. and H.Z-L. Writing—review and editing: X.F. and X.K-L. Visualization: Q.M. Supervision: Q.M. and F.M-Y. Funding acquisition: C.Z. and F.M-Y. All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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