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REVIEW

Roles of Wnt/β-Catenin Signaling Pathway Regulatory Long Non-Coding RNAs in the Pathogenesis of Non-Small Cell Lung Cancer

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Abstract: Lung cancer is one of the leading causes of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer. Long non-coding RNAs (lncRNAs) are promising novel diagnostic and prognostic biomarkers, as well as potential therapeutic targets for lung cancer. Long non-coding RNAs (lncRNAs) have been demonstrated to modulate tumor cells proliferation, cell cycle progression, invasion, and metastasis by regulating gene expression at transcriptional, post-transcriptional, and epigenetic levels. The oncogenic aberrant Wnt/β-catenin signaling is prominent in lung cancer, playing a vital role in tumorigenesis, prognosis, and resistance to therapy. Interestingly, compelling studies have demonstrated that lncRNAs exert either oncogenic or tumor suppressor roles by regulating Wnt/β-catenin signaling. In this review, we aim to present the current accumulated knowledge regarding the roles of Wnt/β-catenin signaling-regulated lncRNAs in the pathogenesis of non-small cell lung cancer (NSCLC). Better understanding of the effects of lncRNAs on Wnt/β-catenin signaling might contribute to the improved understanding of the molecular tumor pathogenesis and to the uncovering of novel therapeutic targets in NSCLC.

Keywords: long non-coding RNA, lung cancer, non-small cell lung cancer, pathogenesis, Wnt/β-catenin signaling

Introduction

Lung cancer is one of the most common cancers, exhibiting high mortality, thus posing a great threat to public health. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases, including squamous cell carcinoma, lung adenocarcinoma (LAD), and large cell carcinoma; whereas the remaining 15% is comprised by small cell lung cancer.[1] Despite the prolific research on lung cancer, its pathogenesis has remained insufficiently known and the merely 15% 5-y survival rate of lung cancer patients has not been improved.[2] Therefore, more studies should be undertaken to explore the pathogenesis of lung cancer, to find early diagnosis biomarkers, and to develop new strategies for treatment.

Long non-coding RNAs (lncRNAs), which have limited protein-coding potential, are a subclass of RNAs with a length greater than 200 nucleotides.[3] Originally regarded as "transcription noise", lncRNAs were found to regulate transcription and translation of protein-coding genes in diverse biological processes through multiple mechanisms. Growing evidence has shown that lncRNAs play a pivotal role in regulating chromatin modification or structure, transcription, splicing, and translation,[4] thereby implicating

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them in the initiation and development of various diseases, notably as well in the tumorigenesis.[5] LncRNAs have been considered as novel biomarker candidates for lung cancer because of their roles in regulating various oncogenic pathways,[6–9] one of which is the Wnt/β-catenin signaling pathway. This pathway has been known to be involved in cell proliferation, invasion,[10] cancer stem cell character,[11] chemotherapy resistance,[12] and epithelial-mesenchymal transition (EMT) process.[13] Given the crucial roles of Wnt/β-catenin signaling and lncRNAs in the malignant tumor, there have been numerous studies on Wnt/β-catenin signaling regulatory lncRNAs. The regulation of Wnt/β-catenin signaling by lncRNAs has been known to efficiently modulate tumorigenesis in cervical,[14] colorectal,[15] laryngeal,[16] breast,[17] liver,[18] and brain cancers.[19] The foci of our review are the roles of Wnt/β-catenin signaling regulatory lncRNAs in the pathogenesis of NSCLC.

LncRNAs in NSCLC

Long non-coding RNAs perform a multitude of functions in regulating the cellular processes in NSCLC, such as proliferation, cell cycle, apoptosis, invasion, EMT,[20] and cancer stem cell (CSC) trait.[21] Mechanistically, lncRNAs are involved in multiple cellular processes, such as chromatin modification, transcriptional modulating, posttranscriptional processing, and protein metabolism, by interacting with DNA, RNAs, and proteins in the nucleus or cytoplasm.[22] Responding to divers stimuli, lncRNAs serve as signaling transducers by molecular decoys, guides, and scaffolds. Furthermore, decoy lncRNAs regulate gene expression by binding to RNA polymerase II, transcription factors (TFs), microRNAs, and target proteins.[23] Guide lncRNAs bind to protein and direct the localization of ribonucleoprotein complex and epigenetic modifiers to target genes. Scaffold lncRNAs recruit different effectors to their molecular partners to facilitate complex formation, consequently controlling downstream pathways.[20] The rapid development of high-throughput platforms has resulted in further understanding the involvement of numerous lncRNAs in the pathogenesis of lung cancer.[24] An example of the oncogenic type is the myocardial infarction-associated transcript (MIAT) whose over-expression is correlated with the growth and migratory abilities of NSCLC cells and with the progression of tumor growth. Hence, MIAT can serve as a critical prognostic biomarker and therapeutic target for NSCLC.[25] In recent studies, forkhead box class O1 (FOXO1) was found to be less expressed in NSCLC tissues than in healthy tissues. The over-expression of FOXO1 inhibits the migration of NSCLC cells in vitro and curbs the growth of tumor in vivo, whereas the silencing of FOXO1 promotes the proliferation and migration of NSCLC cells. These findings substantiate the potential of FOXO1 as a key regulator of lung cancer and as a therapeutic target for NSCLC.[6,26] In addition to Wnt signaling, lncRNAs participate in the pathogenesis of NSCLC by various downstream pathways, such as PI3K/AKT,[6] Hippo,[8] Akt/mTOR,[27] JAK/STAT3,[9] and ERK/MAPK[28] signaling pathways.

Wnt/β-Catenin Signaling Pathway in NSCLC

Wnt signaling is classified into the canonical β-catenin-dependent pathway, and non-canonical β-catenin-independent pathway.[29] In the absence of Wnt ligands, the axis inhibition protein 1 (AXIN1), adenomatous polyposis coli (APC), and glycogen synthase kinase 3β (GSK3β) form a β-catenin destruction complex, which binds to β-catenin and is subsequently phosphorylated by GSK3β. The phosphorylated β-catenin is ubiquitinated and degradated.[29] However, in the presence of Wnt, the complex binds to the frizzled (FZD) family of receptors[30] and lipoprotein receptor-related protein (LRP) co-receptor, resulting in the phosphorylation and activation of the scaffolding protein disheveled (DVL). Consequently, DVL binds to AXIN1, which inhibits GSK3β, subsequently reducing the phosphorylation or proteolytic destruction of β-catenin.[29] The intracellular β-catenin scaffold protein, which is encoded by the *CTNNB1* gene,[31] accumulates in the cytoplasm and subsequently localizes in the nucleus, where it forms a complex with T-cell factor/lymphocyte enhancer factor (TCF/LEF) TFs,[29] eventually activating the transcription of target genes, including cyclin D1 (CCND1) and c-myc.[30] The aberrant activation of the Wnt/β-catenin signaling pathway is integral in NSCLC initiation, progression, metastasis, recurrence, and chemo-resistance.[10]

Mechanisms and Functions of the Wnt/β-Catenin Pathway-Related lncRNAs in NSCLC

Wnt/β-catenin pathway-related lncRNAs are capable of directly or indirectly stimulating one or more components of the Wnt/β-catenin pathway, thereby activating or inhibiting the activity of the pathway. Depending on their function, lncRNAs are either oncogenic or tumor-suppressive. For instance, the long intergenic non-protein coding

RNA00673-v4 (LINC00673-v4) augments TCF/LEF activity and enhances the binding of DEAD-box helicase 3 X-linked (DDX3) and casein kinase 1 (CK1), subsequently triggering Wnt/β-catenin signaling. Over-expressed LINC00673-v4 results in the invasion and migration of tumor cells. Additionally, both clinical data and experimental research validated the positive correlation of LINC00673-v4 expression with the expression of nuclear β-catenin, vascular endothelial growth factor, TWIST1, homeobox B9 (HOXB9), and matrix metalloproteinase-9 (MMP-9).[32] However, lncRNA-SVUGP2, as a tumor suppressor lncRNA, markedly increases the AXIN1 level and decreases the expression of TCF4 and β-catenin, suggesting that SVUGP2 abolishes the briskness of Wnt/β-catenin signaling. Furthermore, SVUGP2 inhibits EMT by increasing E-cadherin and decreasing N-cadherin, vimentin, and snail protein levels. So, lncRNA-SVUGP2 induces apoptosis, inhibits proliferation, and suppresses migration and invasion of NSCLC cells.[33] Generally, these Wnt/β-catenin pathway-related lncRNAs influence the development and prognosis of NSCLC by modulating cell proliferation, invasion, CSC trait and treatment resistance.

Cell Proliferation

Studies have shown that the Sry-like high-mobility group box (SOX) *9*, which is the target gene of miR-101, effectively maintains its oncogenic role in gastric, prostate, intestinal, and lung cancers by activating Wnt/β-catenin signaling.[34] The small nucleolar RNA host gene 1 (SNHG1) promotes the expression of SOX9 by acting as a competing endogenous RNA (ceRNA) for miR-101-3p, subsequently activating Wnt/β-catenin pathway. Both in vitro and in vivo, knockdown SNHG1 significantly suppresses NSCLC cell proliferation by inducing cell apoptosis and causing G1/G0 phases arrest.[35] Similarly, lncRNA SNHG20 enhances nuclear translocation of β-catenin and down-regulates TCF and LEF1 by binding to miR-197. LncRNA SNHG20 facilitates NSCLC cells proliferation and inhibits apoptosis via abnormal activation of Wnt/β-catenin signaling.[36] The over-expression of lncRNA FOXD2-AS1 in NSCLC cells increases the expressions of β-catenin and TCF1 proteins, which are both crucial adaptors of Wnt/β-catenin signaling. The treatment of FOXD2-AS1 over-expressing NSCLC cells with ICG-001, a Wnt/β-catenin signaling inhibitor, repressed the growth of NSCLC cells. However, the administration of SKL-2001, a Wnt/β-catenin signaling activator, prevented NSCLC cell apoptosis induced by the FOXD2-AS1 knockdown. These findings indicate that FOXD2-AS1 facilitates NSCLC tumorigenesis by regulating the Wnt/β-catenin pathway.[37] Further studies showed that LOC730101 induces NSCLC cell proliferation and cell cycle transition from G0/G1 to S stage by promoting the expression of CCND1 and cyclin E1 (CCNE1), which are the target genes of Wnt signaling. The depletion of LOC730101 remarkably reduces the expression of nuclear β-catenin, whereas the administration of IWR-1-endo, a β-catenin inhibitor, obstructed the promotive effect of LOC730101 in H2122 cells.[38] Concomitantly, the silence of lncRNA ASB16-AS1 attenuates proliferation, accelerates apoptosis, and arrests cell cycle in G0/1 phase of NSCLC cells. However, over-expressed ASB16-AS1 up-regulates key proteins in the Wnt/β-catenin pathway, such as β-catenin and cyclin D1.[39] AWPPH, a newly discovered lncRNA, was found to improve proliferation and inhibit apoptosis by aberrantly activating the Wnt/β-catenin signaling in NSCLC cells.[40]

Cell Metastasis and Invasion

Wnt/β-catenin signaling pathway promotes EMT by decreasing E-cadherin and increasing the repressors of adhesion molecule, such as TFs SNAI1, SNAI2 and zinc finger E-box binding homeobox 1 (ZEB1). EMT enhances metastasis and invasion properties of malignant cells, leading to vital organs infiltration and cancer deaths.[10] SOX4 has been suggested to promote tumorigenesis by stimulating Wnt signaling.[41] The silence of FLVCR1-AS1 inhibits proliferation and migration of SPCA1 and A549 cells, resulting in Wnt/β-catenin signaling abrogation by notably down-regulating target genes, such as *CTNNB1, SOX4*, cyclin D1, cyclin D2 (*CCND2*), and *c-myc* in SPCA1 and A549 cells.[42] GSK3β, which is regulated by the lncRNA MIR31HG,[43] the long intergenic non-protein coding RNA 968 (LINC00968; also known as LOC554202)[44] and lncRNA JPX,[45] is an important component of the Wnt/β-catenin signaling pathway. Studies have shown that the knockdown of MIR31HG represses Wnt/β-catenin signaling through down-regulating the expression of GSK3β and β-catenin, but increasing the phosphorylation of GSK3β in NSCLC cells. The down-regulation of MIR31HG reduces proliferation, migration, and EMT in NSCLC cells.[43] The down-regulation of LINC00968 induces the apoptosis of A549 cells by inhibiting the expression of BCL2 apoptosis regulator (BCL-2) while promoting the expression of BCL2-associated X apoptosis regulator (BAX). Decreased LINC00968 also down-regulates β-catenin and cyclin D1

proteins and up-regulates GSK3β protein level in A549 cells. Meanwhile, the silencing of LINC00968 considerably inhibits NSCLC tumor progression in xenograft mouse model.[44] LncRNA JPX promotes cell proliferation and invasion of NSCLC cells by acting as a sponge for miR-33a-5p and up-regulating its target gene, Twist 1. Twist1 directly activates Wnt/β-catenin signaling by increasing β-catenin and decreasing GSK3β.[45]

Based on the notion that dickkopf-related protein 1 (DKK1) is a classical Wnt antagonist,[46] experiments with LAD cells determined that STAT1-activated LINC00467 is located in the cell nucleus, and that it epigenetically silences DKK1 by recruiting the enhancer of zeste homolog 2 (EZH2) protein to the DKK1 promoter. Hence, LINC00467 promotes LAD progression by negatively regulating DKK1 to activate the Wnt/β-catenin pathway.[47] Correspondingly in another study, lncRNA FEZF1-AS1 could bind to EZH2 and to lysine-specific histone demethylase 1A (LSD1), thereby reducing their binding to the E-cadherin promoter regions. FEZF1-AS1 could enhance the EMT process in NSCLC cells by decreasing the expression of E-cadherin and AXIN1 while increasing the expression of β-catenin, TCF4, Slug, TWIST1 and vimentin.[48] Moreover, a separate study revealed that the ability of brain cytoplasmic RNA 1 (BCYRN1) to induce NSCLC cell proliferation and invasion is primarily due to the elevated expression of cell cycle-related proteins CDK4 and some crucial components of the Wnt/β-catenin signaling, such as cyclin D1, β-catenin and c-myc.[49] Interestingly, the transcription factor ELK1 up-regulates HOXA10-AS, a kind of homeobox cluster-embedded lncRNA (HOX-lncRNAs), leading to increased levels of N-cadherin, Slug, β-catenin, and c-myc, and to decreased level of E-cadherin. The Wnt/β-catenin signaling inactivity induced by the silenced HOXA10-AS is reversed with LiCl (an activator of Wnt/β-catenin pathway) treatment.[50] LncRNA X-inactive specific transcript (XIST) up-regulates ring finger protein 1 (RING1) by serving as an ceRNA down-regulating miR-744. Furthermore, RING1 activates Wnt/β-catenin pathway by increasing expression levels of β-catenin, c-myc and cyclin D1, and decreasing E-cadherin expression.[51] A recently published work identified that lncRNA PDIA3P-silencing inhibits growth and invasion of lung cancer by reducing β-catenin and c-myc.[52]

On the other hand, tumor-suppressive lncRNAs have been reported to inhibit Wnt/β-catenin pathway in NSCLC patients. LINC00222 over-expression reduces the phosphorylation of GSK3β and directly enhances its activity, subsequently inactivating Wnt/β-catenin pathway.[53] The LINC00261 promotes the apoptosis of A549 and H1299 cells, impedes cell cycle at the G0/G1 phase, and decelerates cell cycle at the S phase. Functional studies have revealed that LINC00261 sponges miR-522-3p and up-regulates the secreted frizzled-related protein 2 (SFRP2), which is generally regarded as a Wnt signaling suppressor, thereby decreasing the protein expression levels of β-catenin, c-myc, and cyclin D1.[54] Intriguingly, the lncRNA low expression in tumor (LET) inhibits LAD cell proliferation, invasion, and migration by negatively regulating EMT and partly controlling the Wnt/β-catenin pathway. More specifically, the lncRNA LET elevates the level of E-cadherin and reduces the levels of N-cadherin, c-Myc, and nuclear β-catenin in A549 cells.[55]

Cancer Stemness

Wnt/β-catenin signaling plays a determining role in CSCs maintenance. CSCs have the ability of self-renewal and frequently undergo symmetric division, which augments the stem cell pool. CSCs play an important role in the survival, metastasis and recurrence of tumors. Quiescence of CSCs makes cancer resistant to therapy.[56] The transcription factor SOX2 activates Wnt/β-catenin pathway, which enables SOX2 involvement in EMT modulation, and sustaining CSC potency.[57] The carcinogenic colon cancer associated transcript 1 (CCAT1) increases the expression levels of MYC proto-oncogene, SOX2 and TCF4 and activates Wnt signaling in A549 and H460 cell lines. Subsequent research showed that miR-Let-7c could bind to CCAT1, resulting in the abolition of the CCAT1-induced symmetric division and of the self-renewal activity of lung CSCs.[57] The nuclear-enriched abundant transcript 1 (NEAT1) up-regulates SOX9 expression by ceRNA for miR-101-3p.[58] NEAT1 also increases the β-catenin and p-GSK3β protein levels but diminishes the p-β-catenin and GSK3β levels in A549/CDDP cells.[59] Thereby, NEAT1 results in the activation of Wnt/β-catenin signaling.[60] NEAT1 contributes to the CSC phenotype in NSCLC by inhibiting epigallocatechin gallate (EGCG)-upregulated copper transporter 1 (CTR1)[61] and activating Wnt/β-catenin pathway.[59] In addition, lncRNA MIR4435-2HG promotes the transactivation of β-catenin, and prevents its degradation in H1650 and H1299 cells. MIR4435-2HG positively regulates invasion and EMT of lung cancer cells by down-regulating E-cadherin and up-regulating vimentin, N-cadherin, and TWIST1.[62] Both of β-catenin and EMT bestow cancer cells with CSC-like

traits.[63] MIR4435-2HG dramatically inhibits spheroid formation and is implicated in CSC traits in tumor cells.[62]

Therapy Resistance

Wnt signaling can affect the resistance to cisplatin (CDDP), docetaxel, and radiotherapy, rendering the administration of Wnt inhibitors to restore sensitivity.[64] In specimens of resected NSCLC, proteins Wnt-1, Wnt-2, Wnt-3, Wnt-5a, and Wnt-11 were over-expressed, and their expression positively correlated with the activation of Wnt/β-catenin pathway.[65] The oncogenic urothelial carcinoma associated 1 (UCA1) increases the expression of Wnt-3a, Wnt-5a and β-catenin proteins, thereby stimulating Wnt signaling activity and reversing the anti-tumor effect of curcumin in NSCLC cells. The same study further reported that UCA1 affects the incidence and progression of lung cancer by regulating the mTOR pathway.[66] Interestingly, UCA1 also induces the resistance of A549/DDP cells to DDP by promoting EMT.[67] The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) functions as a ceRNA in DDP-resistant cancer cells by sponging miR-101, thereby up-regulating SOX9 expression and activating Wnt signaling. In return, SOX9 activates MALAT1 transcription by binding to its promoter. Hence, MALAT1, miR-101 and SOX9 form a feedback loop that results in the enhancement of the DDP resistance of LAD cells.[68] To corroborate the findings on the treatment resistance effects of Wnt/β-catenin signaling-related oncogenic lncRNAs, a number of studies were performed on the mechanisms by which the homeobox transcript antisense ribonucleic acid (HOTAIR) is able to promote NSCLC progression. The reduced expression of HOTAIR clearly down-regulates the expression of Wnt-3a, β-catenin, and APC proteins and inhibits the activation of Wnt/β-catenin pathway. Additionally, the knockdown of HOTAIR significantly increases the sensitivity of cells to DDP via decreasing classical multidrug-resistant proteins, including multidrug resistance-associated protein 1 and multidrug resistance 1.[69] Over-expressed HOTAIR obviously reduces tumor radio-sensitivity by decreasing Wnt inhibitory factor 1 expression, which is an Wnt/β-catenin signaling inhibitor.[63] A recent study revealed that lncRNA AK126698 negatively regulates the components of Wnt/β-catenin signaling, such as FZD8, β-catenin, c-myc, and CNND1 proteins. In contrast, knockdown of AK126698 induces cisplatin resistance by activating Wnt signaling in A549 cells.[70,71] In the same way, the maternally expressed gene 3 (MEG3) triggers the transcriptional activation of the tumor suppressor gene p53, which down-regulates the expression of β-catenin/survivin through the activation of GSK3β and ubiquitin-proteasome system. Thus, MEG3 can induce apoptosis, regulate cell cycle and decrease drug resistance in NSCLC cells by inhibiting Wnt/β-catenin signaling.[72]

Wnt/β-Catenin Pathway-Related lncRNAs: Biomarkers of Tumor Diagnosis and Prognosis

LncRNAs can be exploited as promising biomarkers for diagnosis and prognosis due to their stability[73] and their specificity in expression profile. Specifically, compared with mRNA, lncRNA expression is more specific in cells, tissues, developmental stage and diseases state.[74] These Wnt/β-catenin signaling-related lncRNAs have been proved to be differently expressed between lung cancer tissues and adjacent noncancerous tissues, including 23 up-regulated oncogenic lncRNAs and 6 down-regulated tumor suppressive lncRNAs. For instance, the high expression of XIST is in correlation with carcinoembryonic antigen (CEA) level, tumor size, TNM stage, distant metastasis. XIST is thought of as being a marker of diagnostic for NSCLC.[51] Apart from tissues, lncRNAs are also present in blood and sputum and are considered as invasive biomarkers. LncRNA SNHG1 and HOTAIR in sputum are identified as biomarkers for diagnosis of lung cancer, producing 82.09% sensitivity and 89.23% specificity. Compared with sputum cytology, the biomarker panels of SNHG1 and HOTAIR have higher sensitivity and similar specificity.[75] The plasma HOTAIR level is line with the TNM stage, and has a high positive diagnostic efficiency of NSCLC. The ROC curves show that the area under curve (AUC) of HOTAIR for NSCLC patients versus healthy controls is 0.791 (95% CI: 0.727–0.855), which is higher than CEA (AUC = 0.737, 95% CI: 0.666–0.808).[76] The ROC analysis illustrated that the combination of serum CCAT1 and SOX2OT yield an AUC of 0.894 (95% CI: 0.825–0.963; $P < 0.001$), which has a high diagnostic accuracy.[77] In addition to lncRNAs used for the differentiation of NSCLC, they also have prognostic relevance. Correlation analyses of clinical data suggest HOTAIR,[66] MIR31HG,[43] HOXA10-AS,[50] LINC00467,[47] LINC00261[54] and LINC00222[53] can be used as prognostic factors for NSCLC patients. Specifically, multivariate analysis confirm XIST,[51] UCA1[66] and MALAT1[78] expression levels are independent predictive factors for poor overall survival rate. The clinical significance of lncRNAs

are still unclear and requires larger clinical data validation and follow-up investigation.

Wnt/β-Catenin Pathway-Related lncRNAs: Potential Therapeutic Targets

Given their versatile regulatory function, lncRNAs may be potential therapeutic targets. Currently, some technologies, including antisense oligonucleotides (ASOs) and RNAs interference (RNAi), have been used to inhibit cancer development and metastasis.[79] ASO is more suitable for clearing the nuclear lncRNAs (MALAT1 and NEAT1). The lncRNA in cytoplasm is more efficiently suppressed by RNAi. RNAi and ASOs are both able to reduce HOTAIR (dual-localized lncRNA). However, ASOs achieves an overall higher level of knockdown.[80] MALAT1 ASOs exerts a potent anti-metastatic activity in lung cancer xenograft tumors, suggesting that MALAT1 can be a promising therapeutic target.[81] To date, pre-clinical studies on targeting lncRNAs for NSCLC therapy remain limited. Although some tumor-associated lncRNAs such as MALAT1 and NEAT1 are well conserved, there is a lack of conservation for many lncRNAs between human and mouse.[79] LncRNAs can be knocked down by traditional siRNA in cell lines. However, experiments using siRNAs are still challenging in vivo. There are two main reasons for this, one is the lack of superior delivery methods, and the other is limited bioavailability of siRNAs in vivo.[82,83] SiRNA can be packaged in synthetic carriers to enter the cell membrane, such as lentiviral vector, liposome carrier and nanoparticles.[84] More research are required to construct high-quality vector of RNAi regents for more effective target action. Overall, targeting lncRNAs for tumor treatment is a promising therapy because of their stability, target specificity, efficacy, and few side effects.[85]

LncRNAs as Wnt/β-Catenin Pathway Effectors in Cancer

Recent research has found that lncRNAs not only regulate Wnt/β-catenin pathway but also function as its targets.[86] For instance, in colorectal cancer, lncRNA CASC11 interacts with heterogeneous ribonucleoprotein K, which induces the shuttling of β-catenin to nucleus and promotes its target gene expression. Hence, CASC11 activates Wnt/β-catenin pathway and exerts as oncogenic function by up-regulating c-myc, CCND1 and MMP7. In return, c-myc binds to the promoter of CASC11, increases promoter acetylation, and enhances its expression. Obviously, there is a positive regulatory feed-forward loop between CASC11 and c-myc.[87] Still in colorectal cancer, lncRNA CCAT2 physically binds to the TCF4 transcription factor and up-regulates its transcriptional activity, subsequently leading to the Wnt/β-catenin pathway activation. TCF4 also interacts with the TCF4 element located within SNP rs6983267, which expresses lncRNA CCAT2.[88] Although the functions of some lncRNAs can be partly reversed by Wnt/β-catenin pathway inhibitors, such as LOC730101, HOTAIR, and FOXD2-AS1, above-mentioned Wnt/β-catenin pathway-related lncRNAs have not been reported to be regulated by this pathway.

Others

Despite the aforementioned studies regarding the lncRNAs directly involved in the regulation of the Wnt/β-catenin pathway, there are still many other lncRNAs reported to modulate the key components of the Wnt/β-catenin signaling pathway. For example, the cancer susceptibility candidate 9.5 (CASC9.5) has been shown to play a tumor-promoting role in LAD progression by regulating the expression levels of cyclin D1, E-cadherin, N-cadherin, and β-catenin.[89] Similarly, HNF1A-AS1 was found to facilitate cancer progression, both in vitro and in vivo, by modulating cyclin D1, E-cadherin, N-cadherin and β-catenin expression.[90] Moreover, the reduced expression of phosphorylated-ERK1/2 (p-ERK1/2) and β-catenin exposes the role of CASC2c as a tumor suppressor lncRNA in NSCLC, inhibiting the proliferation and migration of NSCLC cells.[91] Another lncRNA RP11-713B9.1, which is the antisense transcript of tumor suppressor in lung cancer 1 (TSLC1), apparently enhances the expression of TSLC1, CYLD lysine 63 deubiquitinase (CYLD), and APC, which negatively regulates Wnt signaling.[92] Despite the wealth of the data presented here, it is imperative that the relationship between the aforementioned lncRNAs and Wnt/β-catenin pathway to be further investigated.

Conclusion and Perspective

Numerous oncogenic or tumor suppressor lncRNAs affect the proliferation, apoptosis, migration, and metastatic spread of NSCLC cells by modulating the Wnt/β-catenin signaling pathway (Table 1). The Wnt/β-catenin pathway is extensively involved in normal tissue development and, most prominently, in cancer. Interestingly, the same lncRNA regulates Wnt/β-catenin signaling by diversified mechanisms and even participates in the progression of NSCLC by other signaling pathways (Figure 1). A number

Table 1 The Components, Method, Mechanisms, and Clinical Features of the Interactions of Long Noncoding RNAs (lncRNAs) with the Wnt/β-Catenin Signaling Pathway in the Pathogenesis of NSCLC

Effect	lncRNA	Method	Bind To	Associated Clinical Feature	Associated Cell Process	Ref
Oncogenic	CCAT1	qRT-PCR	SOX2	Higher risk of death	CSC traits	93
	FLVCR1-AS1	Microarray and qRT-PCR	SOX4	Advanced TNM stage and lymph node metastasis	Promotes cell proliferation, migration and invasion	55,94
	NEAT1	qRT-PCR	SOX9	Advanced TNM stage, and lymph node metastasis	Promotes cell proliferation, invasion and CSC traits	58
	MALAT1	qRT-PCR	SOX9	Distant metastasis, lymph node metastasis, advanced TNM stage, and poor prognosis	Promotes cell proliferation, migration, invasion, and chemo-resistance	68
	SNHG1	Microarray and qRT-PCR	SOX9	Advanced TNM stage, lymph node metastasis, and shorter survival time	Promotes cell proliferation	35
	UCA1	NGS	Wnt	Advanced TNM stage, lymph node metastasis, and poor overall survival	Promotes cell viability and drug resistance	66,95
	HOTAIR	qRT-PCR	Wnt	Lymph node metastasis, TNM stage, and poor survival rate	Promotes therapy resistance	69
	AWPPH	qRT-PCR	-	Shorter survival and poor prognosis	Promotes cell proliferation	40
	FOXD2-AS1	Microarray	TCF1	Advanced stage, and poor prognosis	Promotes cell proliferation	37
	FEZF1-AS1	qRT-PCR	AXIN1	Poor differentiation grade, lymph node metastasis, advanced TNM stage, and poor prognosis	Promotes cell proliferation, migration, and invasion	48
	LINC00968	Microarray	GSK3β	Poor prognostic outcomes	Promotes cell proliferation, migration, and invasion	44
	MIR31HG	qRT-PCR	GSK3β	Poor histological differentiation grade, lymph node metastasis, and advanced TNM stage	Promotes cells viability, proliferation, and invasion	43
	JPX	qRT-PCR	GSK3β	Lymph node metastasis, advanced TNM stage, and poor prognosis	Promotes cell proliferation, migration, and invasion	45
	SNHG20	qRT-PCR	β-catenin	Poor prognosis	Promotes cell proliferation	36
	ASB16-AS1	qRT-PCR	β-catenin	Advanced TNM stage	Promotes cell proliferation	39
	PDIA3P	qRT-PCR	β-catenin	Lymph node metastasis, advanced TNM stage, and poor prognosis	Promotes cell proliferation, migration, and invasion	52
	HOXA10-AS	Microarray and qRT-PCR	β-catenin	Unfavorable prognosis	Promotes cell proliferation and metastasis	50
	LOC730101	Microarray and qRT-PCR	β-catenin	Shorter survival time	Promotes cell proliferation and growth	38
	XIST	Microarray and qRT-PCR	β-catenin	Advanced TNM stage, and poor overall survival	Promotes cell proliferation, migration, and invasion	51
	BCYRN1	qRT-PCR	β-catenin	Poor prognosis	Promotes cell migration and proliferation	49
	MIR4435-2HG	qRT-PCR and NGS	TCF/LEF	Lymph node metastasis and advanced cancer stage	Promotes cell proliferation, invasion, CSC traits, and EMT	62
	LINC00673-V4	Microarray	DVL	Lymph node metastasis and poor prognosis	Promotes cell invasion, migration, and metastasis	32
	LINC00467	Microarray	DKK1	Poor prognosis	Promotes cell proliferation and migration	47
Tumor-suppressing	LINC00261	qRT-PCR	SFRP2	Prognosis	Inhibits cell proliferation and invasion	54
	MEG3	qRT-PCR	GSK3β	Overall survival	Inhibits invasion, migration, and chemo-resistance	72,96

(*Continued*)

Table 1 (Continued).

Effect	lncRNA	Method	Bind To	Associated Clinical Feature	Associated Cell Process	Ref
	LET	qRT-PCR	β-catenin	Tumor stage, and lymph node metastasis	Inhibits cell proliferation and migration	97
	AK126698	Microarray and qRT-PCR	FZD8	Advanced pathologic stage	Inhibits cell proliferation, migration, and therapy resistance	70,71
	SVUGP2	qRT-PCR	AXIN1, β-catenin	Tumor size and clinical stage	Inhibits cell proliferation, invasion, and migration and induces apoptosis	33
	LINC00222	qRT-PCR	GSK3β	Disease-free survival, and overall survival	Inhibits cell proliferation and migration	53

Abbreviations: NGS, next-generation sequencing; qRT-PCR, quantitative reverse-transcription polymerase chain reaction.

of studies has demonstrated that, aside from lncRNAs, certain Wnt pathway factors could also regulate the Wnt pathway by modulating the activity of lncRNAs in other cancers. The effects of the Wnt pathway on lncRNAs in NSCLC and the relationship between them should be further studied. Our literature review elaborated and recapitulated the interactions between lncRNAs and Wnt/β-catenin signaling as well as their involvement in the pathogenesis of NSCLC. The findings discussed here clearly demonstrated that the Wnt/β-catenin signaling pathway-related lncRNAs could be used as potential diagnostic and prognostic indicators and as a novel target for NSCLC therapy. Understanding the relationships among the Wnt/β-catenin signaling, the Wnt/β-catenin pharmacological inhibitors, and the profiles of lncRNAs could pave the way towards the development of novel treatment

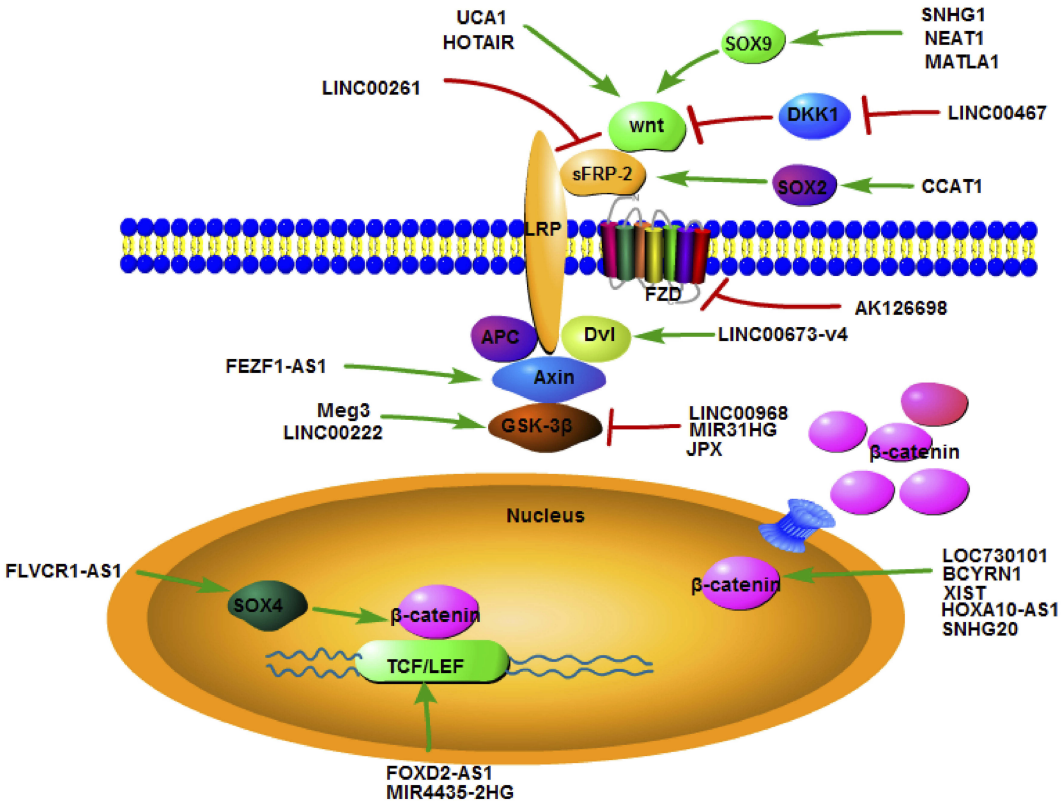

Figure 1 The regulatory functions of oncogenic and tumor suppressor long non-coding RNAs (lncRNAs) in the Wnt/β-catenin signaling pathway attributed to the pathogenesis of non-small cell lung cancer (NSCLC).

options with greater curative efficacy but lesser side effects.

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Disclosure

The authors declare no competing interests.

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