

Exploring the Roles of Wnt Signaling Pathway and Non-Coding RNAs in COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease with one of the leading causes of global morbidity and mortality. Its core pathological features include irreversible airflow limitation, chronic airway inflammation, and lung tissue remodeling. In recent years, the key roles of the Wnt signaling pathway and non-coding RNAs (ncRNAs) in the pathogenesis of COPD have gained increasing attention. As a pivotal signaling cascade governing cell proliferation, differentiation and tissue repair, the Wnt pathway undergoes aberrant activation or suppression in COPD, linking closely to airway inflammation, alveolar epithelial damage and pulmonary fibrosis. Non-coding RNAs including miRNAs, lncRNAs and circRNAs modulate COPD pathogenesis via targeting core molecules of the Wnt pathway. This review summarizes the basic components and functions of the Wnt pathway and the classification and biological roles of ncRNAs and discusses their interactive mechanisms and therapeutic strategies in COPD. In addition, this review discusses the current controversies and future directions. Studies indicate that the synergistic regulatory network between the Wnt pathway and ncRNAs provides new molecular targets for the early diagnosis, prognosis assessment, and targeted therapy of COPD, highlighting potential avenues for future therapeutic development.

Keywords: COPD, Wnt signaling pathway, ncRNAs

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with its prevalence and mortality rates showing a continuous upward trend.^{1,2} Recent studies have shown that COPD is the third leading cause of death worldwide, posing a serious threat to human health and representing a major public health issue.³ COPD affects 13.1% of people worldwide and 13.7% of Chinese people over 40 years old.^{4,5} To date, the etiology of COPD remains unclear. Current studies indicate that the development and progression of COPD result from the interplay of genetic and environmental factors.⁶ Studies have indicated that genetic predisposition plays a significant role in COPD pathogenesis. For instance, genome-wide association studies (GWAS) have identified multiple genetic loci associated with COPD that may increase an individual's disease risk by influencing lung function and disease progression.⁷ Additionally, variations in specific genes, such as SERPINA1, EPHX1, GST, MMP12, TGF- β 1, and SERPINE2 have been linked to susceptibility to COPD.^{6,8,9} Environmental factors also play a critical role in COPD development. While smoking is the primary environmental risk factor, other factors, such as air pollution, occupational exposure, and biomass fuel use are also recognized as significant environmental risk factors.¹⁰ These epidemiological characteristics suggest that the prevention and management of COPD requires comprehensive consideration of environmental exposure, genetic susceptibility, and comorbidity management.

The molecular mechanisms underlying COPD involve multiple signaling pathways and molecular regulatory networks. Recent studies have indicated that the Wnt signaling pathway, non-coding RNAs (nc-RNAs), and their interactions may serve as key molecular bridges connecting these risk factors to disease progression.^{11–13} MicroRNAs (miRNAs) participate in the inflammatory response and airway remodeling in COPD by regulating the expression of

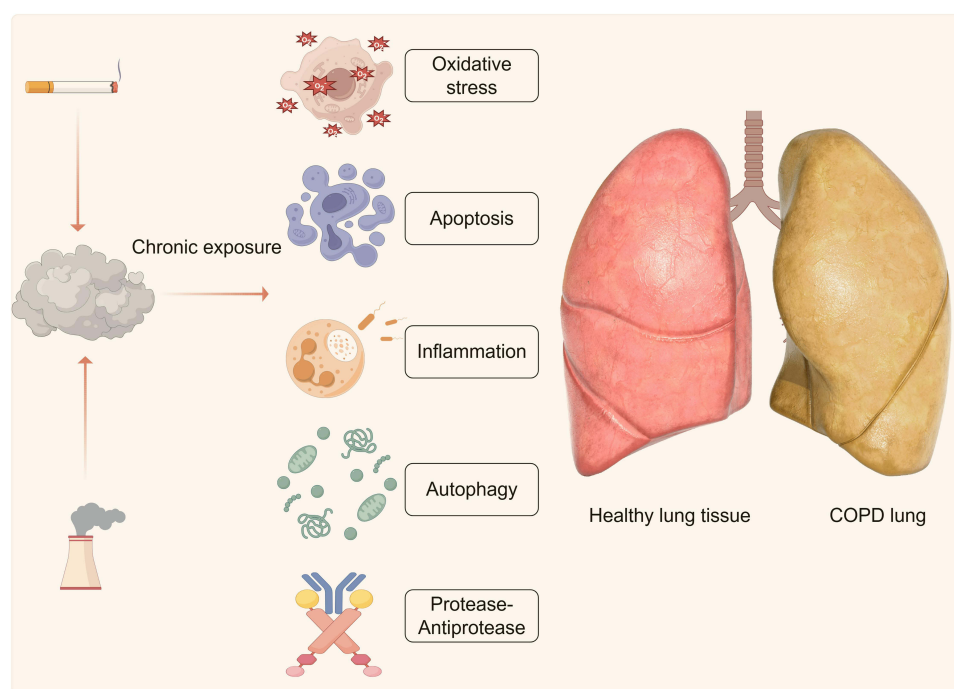


Figure 1 The etiology of COPD. Chronic exposure to smoke can induce oxidative stress, apoptosis, inflammation, autophagy, and protease-antiprotease biological process. These contribute to the development of COPD.

target genes. For example, miR-29c and miR-126 are significantly downregulated in patients with COPD and are associated with disease severity.¹³ Additionally, long non-coding RNAs (lncRNAs), such as MALAT1 and TUG1 are involved in the pathogenesis of COPD.^{14,15} For example, lncRNA TUG1 is significantly upregulated in the lung tissues of patients with COPD and promotes airway remodeling by regulating the miR-145-5p/DUSP6 axis. Aberrant activation of the canonical Wnt/ β -catenin pathway is associated with airway smooth muscle hyperplasia and fibrosis in COPD patients. For instance, β -catenin expression is significantly elevated in airway smooth muscle cells of patients with COPD and is positively correlated with airway wall thickness.¹⁶ The non-canonical Wnt pathway, such as the Wnt5a pathway, is also involved in the pathogenesis of COPD. Wnt5a expression is significantly upregulated in the lung tissues of patients with COPD and promotes emphysema formation by inhibiting the classical Wnt pathway.¹⁷ These results indicate that abnormal regulation of nc-RNAs and the Wnt pathway is a critical component in the pathological progression of COPD. Although increasing studies have confirmed that the interaction between non-coding RNAs and the Wnt signaling pathway regulates the occurrence and progression of COPD, relevant reviews summarizing their interaction mechanisms are still lacking. Therefore, this review aimed to elucidate the pivotal role of the ncRNA-Wnt signaling axis in COPD, highlighting potential avenues for future therapeutic development (Figure 1).

Wnt Signaling Pathway and COPD

Basic Components and Function of the Wnt Signaling Pathway

The Wnt signaling pathway is a highly conserved signaling transduction pathway that plays a central role in embryonic development, tissue homeostasis maintenance, tissue regeneration, and disease pathogenesis.^{18–20} It is primarily classified into three major branches: the canonical Wnt/ β -catenin signaling pathway, the non-canonical planar cell polarity (PCP)/Wnt signaling pathway, and the non-canonical calcium-dependent Wnt signaling pathway.²¹ Canonical Wnt/ β -catenin signaling pathway is dependent on β -catenin.²² However, the non-canonical Wnt signaling pathway is not dependent on β -catenin activation.²³ Activation of the canonical Wnt signaling pathway depends on the binding of Wnt ligands to transmembrane co-receptors composed of the Frizzled (FZD) receptor and low density lipoprotein receptor-related protein 5 or 6 (LRP5/6), which inhibit the activity of the β -catenin degradation complex (composed of adenomatous

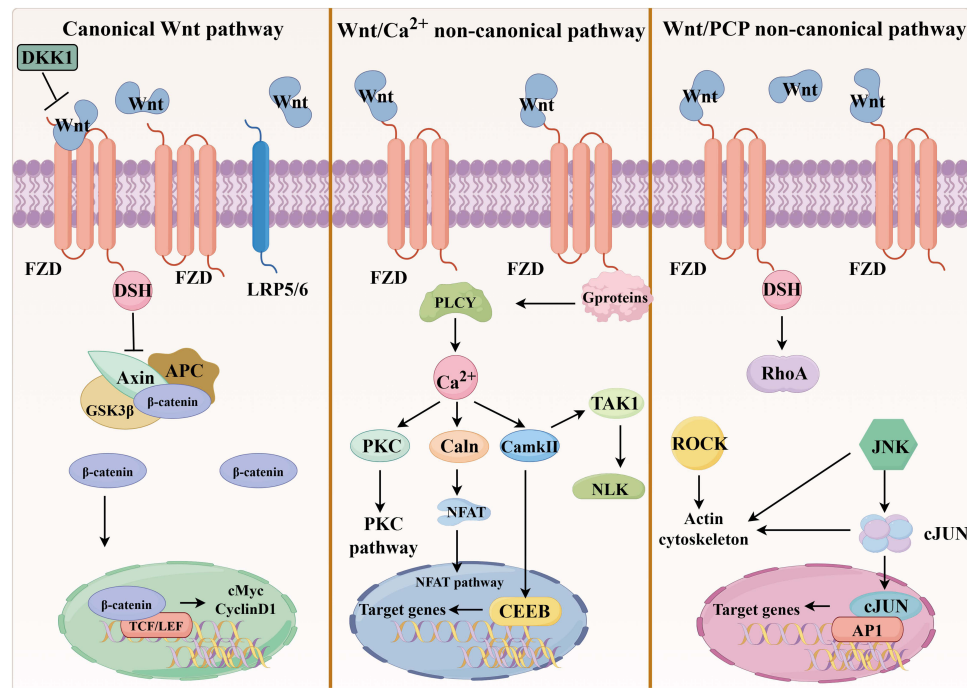


Figure 2 The Wnt signaling pathway. It is primarily classified into three major branches: the canonical Wnt/ β -catenin signaling pathway, the non-canonical calcium-dependent Wnt signaling pathways, and the non-canonical PCP/Wnt signaling pathway.

polyposis coli (APC), glycogen synthase kinase 3 protein (GSK3), AXIN, etc), leading to the accumulation of β -catenin in the cytoplasm and its entry into the nucleus. β -catenin binds to TCF/LEF transcription factors to regulate the expression of target genes such as c-Myc and Cyclin D1.²⁴ For example, inhibition of the canonical Wnt signaling pathway promotes epithelial branching during morphogenesis of submandibular gland branches in embryonic mice.²⁵ The non-canonical Wnt signaling pathway regulates cell polarity, migration, and inflammatory responses by activating kinases such as calcium/calmodulin-dependent protein kinase II (CaMKII), c-Jun N-terminal kinases (JNK), and protein kinase C (PKC).²⁶ For instance, Wnt5a promotes chondrocyte degradation in osteoarthritis through a nonclassical pathway²⁷ (Figure 2).

Pathological Role of Wnt Signaling Pathway in COPD

The Wnt signaling pathway plays a complex role in the pathogenesis of COPD, with abnormal activation or inhibition participating in multiple pathophysiological processes. The Wnt signaling pathway regulates the pathogenesis of COPD through multiple mechanisms, such as the inflammatory response, epithelial apoptosis, airway remodeling, and the imbalance of the canonical and non-canonical pathway.^{28–30} These multiple mechanisms may work together to regulate COPD pathogenesis.

The Role of Wnt Signaling Pathway in Inflammatory Response of COPD

The Wnt signaling pathway plays a critical role in the inflammatory response in COPD. Abnormal activation or inhibition can influence the progression of COPD by regulating the infiltration of inflammatory cells and release of inflammatory factors.³¹ Previous studies have confirmed that Wnt4 is upregulated in primary bronchial epithelial cells (PBEC) from patients with COPD and amplifies inflammation triggered by cigarette smoke.^{31,32} Interestingly, it did not affect the canonical WNT target genes but triggered the activation of the non-canonical signaling molecule p38. In addition, activation of the canonical Wnt/ β -catenin pathway can suppress the inflammatory responses in COPD. Studies have shown that Wnt3a can promote the expression of antioxidant enzymes by activating the (nuclear factor erythroid-2 related factor-2) Nrf2 pathway, thereby alleviating oxidative stress-induced inflammation.³⁰ Wnt3a overexpression

significantly reduced IL-6 and IL-8 secretion in human bronchial epithelial cells (NHBE) treated with cigarette smoke extract (CSE), whereas Wnt3a knockdown further increased the secretion of these inflammatory factors.

Activation of the non-canonical Wnt signaling pathway promotes inflammatory responses in COPD. Wnt5a, a key ligand of the non-classical Wnt pathway, exhibits significantly elevated expression in the lung tissues of patients with COPD and can promote the expression of inflammatory factors (such as IL-6 and IL-8) by activating the NF- κ B pathway. In alveolar macrophages of patients with COPD, Wnt5a treatment increased IL-6 secretion.^{33,34} In patients with COPD, the levels of Wnt5a- and Wnt5b-induced IL-6 and CXCL8 secretion in pulmonary fibroblasts were significantly higher than those in healthy controls.³³ Additionally, the Wnt signaling pathway can influence the inflammatory response in COPD by regulating the activation and proliferation of T lymphocytes.

Previous studies have shown that secreted frizzled-related protein 2 (sFRP2) inhibits the Wnt pathway by competitively binding to Wnt ligands of the frizzled protein receptor, thereby exacerbating airway inflammation and disrupting Th17/Treg homeostasis.^{35,36} CSE exposure increases sFRP2 expression, which in turn inhibits Wnt/ β -catenin signaling, leading to Th17 cell expansion and Treg cell suppression. This suggests that sFRP2-induced Wnt suppression is a key driver of Th17/Treg imbalance. Additionally, sFRP2 may indirectly affect T cell balance by modulating dendritic cells (DCs) function. DCs are critical antigen-presenting cells that regulate Th17 and Treg differentiation, and their function is impaired in COPD.³⁷ Results found that COPD patients had reduced mature DC (mDC) levels and increased immature DC (imDC) levels, with a positive correlation between imDC frequency and Th17/Treg ratio. Furthermore, sFRP2 has been shown to regulate macrophage polarization.³⁸ These findings indicate that sFRP2 might also modulate the Th17/Treg balance via inhibiting Wnt signaling pathway in COPD.

The Effect of Wnt Signaling Pathway on Apoptosis in COPD

The Wnt signaling pathway plays a critical role in apoptosis in COPD. Abnormal activation or inhibition can influence cell survival and death in the lung tissue of patients with COPD by regulating the expression of apoptosis-related genes. Previous studies have indicated that inhibition of the Wnt signaling pathway alleviates pulmonary fibrosis by promoting lung fibroblast apoptosis.³⁹ In addition, studies have shown that bone marrow mesenchymal stem cell (BMSCs)-derived exosomes can decrease apoptosis of pulmonary microvascular endothelial cells in CSE-induced COPD by targeting Wnt5a.⁴⁰ In a cigarette smoke-induced COPD mouse model, treatment with the Wnt pathway activator, LiCl, significantly reduced the apoptosis rate of alveolar epithelial cells and improved lung function.³⁰ Similar studies have indicated that activation of the Wnt5a signaling pathway promotes proliferation and inhibits apoptosis of normal lung fibroblasts. This effect is mediated by the non-canonical Wnt signaling pathway.⁴¹

Regulatory Mechanism of Wnt Signaling Pathway in Airway Remodeling of COPD

The Wnt signaling pathway plays a pivotal role in airway remodelling in COPD. Its abnormal activation or inhibition can influence the progression of airway remodeling by regulating the proliferation of airway smooth muscle cells, epithelial-mesenchymal transition (EMT), and extracellular matrix (ECM) deposition.^{28,42-44} Activation of the non-canonical Wnt signaling pathway promotes airway remodeling in COPD. Studies have shown that Wnt5a enhances the proliferation and migration of airway smooth muscle cells by activating the β -catenin pathway.⁴³ In TGF- β 1 induced airway smooth muscle cells, overexpression of Wnt5a significantly increased cell proliferation rate and migration capacity, whereas Wnt5a knockdown markedly reduced these parameters. Additionally, the activation of the Wnt pathway can facilitate EMT and contribute to airway fibrosis. In airway epithelial cells of COPD patients, the expression level of Wnt5a was positively correlated with the expression of EMT-related genes.⁴⁵ Inhibition of the Wnt signaling pathway also inhibits the expression of matrix metalloproteinases (MMPs), degrades the ECM, and leads to airway remodeling damage.⁴⁶ Research has demonstrated that miR-149-3p modulates the expression of Wnt1, Wnt5a, β -catenin, and RhoA, and alters the expression of alveolar inflammatory factors. These alterations subsequently influence the expression of alveolar inflammatory factors, thereby affecting the pathological progression of COPD.⁴⁷⁻⁴⁹ The canonical Wnt signaling pathway also plays an important role in airway remodelling in COPD. Studies have shown that nicotine exposure induces upregulation of Wnt3a and activation of the canonical Wnt signaling pathway, along with an increase in collagen type I, vimentin, and α -SMA, and downregulation of E-cadherin.^{50,51}

Nc-RNAs and COPD

NC-RNA plays multiple roles in the pathological process of COPD, including airway inflammation, oxidative stress, epithelial injury, and airway remodeling. In this section, we summarize the roles of ncRNAs in COPD.

Classification and Biological Functions of Nc-RNAs

Of the diverse RNA families present within cells, long non-coding RNAs (lncRNAs, >200 nt), microRNAs (miRNAs, 20–24 nt), and circular RNAs (circRNAs, covalently closed loop structures) are categorized as nc-RNAs, a class which exerts significant regulatory functions in both fundamental physiological processes and the development of various pathological conditions in humans.^{52–55} miRNAs regulate gene expression by binding to the 3'-UTR of their target mRNA, thereby inhibiting translation or promoting degradation.⁵⁴ lncRNAs exhibit a broad range of functions, including (1) acting as endogenous competing RNAs (ceRNAs) to sponge adsorbed miRNAs and regulate target gene expression; (2) binding to proteins to modulate their localization or activity; and (3) participating in chromatin remodeling.^{56,57} CircRNAs exhibit high stability and function primarily as ceRNAs.

Pathological Role of Nc-RNAs in COPD

Nc-RNAs play crucial regulatory roles in the pathological processes of COPD, with miRNAs and lncRNAs being the most extensively studied. miRNAs regulate gene expression by targeting the 3'-UTR region of mRNA, participating in inflammatory responses, airway remodeling, and apoptosis associated with COPD. Recent studies have confirmed that miRNAs are critical modulators of macrophage activity, demonstrating their capacity to both drive and protect against inflammatory responses.¹² For instance, miR-21 promotes COPD pathogenesis by regulating the SATB1/S100A9/NF- κ B signaling axis. Targeting miR-21 suppresses the inflammatory response and improves lung function.⁵⁸ miRNAs derived from epithelial cell-exosomes, such as miR-125a-5p and miR-221-3p, promote M1 macrophage polarization.^{59,60} Other pro-inflammatory nc-RNAs like miR-486-5p, miR-27-3p, miR-1260, miR-155, and lncRNA MEG3, also regulate macrophages via different signaling pathways.^{12,61–63} In contrast, some miRNAs play a protective role in the inflammatory response and emphysema formation. For example, miR-195-5p, miR-146a, miR-513a-5p, miR-150, miR-344b-1-3p, Cox2, and IL7R inhibit COPD development by targeting NF- κ B and TLR signaling.^{64–70} However, another study showed that M2 macrophage polarization might play a role in promoting rather than inhibiting COPD development by regulating mirR-let-7c.⁷¹ Interestingly, MIR155HG has the ability to regulate in two directions. Overexpression lncRNA MIR155HG promotes M1 macrophages polarization and pro-inflammatory cytokine release, whereas downregulation lncRNA MIR155HG enhances M2 macrophages development.^{72,73} nc-RNAs are a large family of transcripts. However, its role in COPD requires further investigation (Figure 3).

The Interaction Mechanisms Wnt Signaling Pathway and Nc-RNAs in COPD

As reported before, nc-RNAs can promote or inhibit disease development by regulating Wnt signaling pathway.^{21,74,75} However, the crosstalk between the Wnt signaling pathway and nc-RNAs remains unclear. Recent studies have reported that crosstalk between the Wnt signaling pathway and nc-RNAs plays an important role in COPD. In this section, we summarize the role of ncRNAs intertwined with the Wnt signaling pathway in COPD (Table 1).

Interaction between ncRNAs and the Wnt pathway is one of the core mechanisms regulating cell fate and disease progression. lncRNA, as a ceRNA, sponges miRNAs and indirectly regulates the expression of key molecules in the Wnt signaling pathway. The lncRNA GATA3-AS1 is highly expressed in pancreatic cancer, upregulating Tex10 expression by sponging miR-30b-5p and activating the Wnt signaling pathway to promote tumor proliferation.⁷⁹ miRNAs directly target key components of the Wnt signaling pathway. Furthermore, circRNAs are involved in Wnt signaling pathway regulation via sponge adsorption of miRNAs.⁸⁰ The interaction between ncRNAs and the Wnt signaling pathway also involves epigenetic regulation.⁸¹

It has been shown that nc-RNAs could inhibit COPD development by targeting Wnt signaling pathway. Previous studies have indicated that let-7c-3p plays a protective role in COPD by regulating PPAR/RXR, WNT/ β -catenin, and

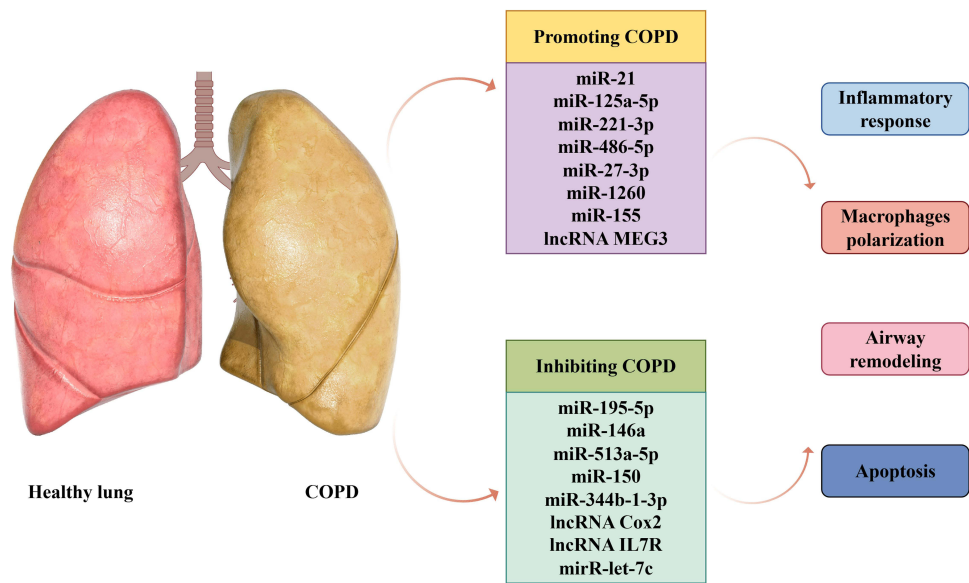


Figure 3 The biological function role of nc-RNAs in COPD. Nc-RNAs participated in the inflammatory responses, airway remodeling, and apoptosis associated with COPD, and nc-RNAs were recognized as critical modulators of macrophage activity, demonstrating a capacity for both driving and protecting against inflammatory responses.

pulmonary fibrosis pathways.⁷⁶ However, the mechanisms by which let-7c-3p regulates the Wnt/ β -catenin signaling pathway have not yet been reported. In patients with CSE-induced COPD, miR-30b was down-regulated.⁴⁰ Overexpression of miR-30b reduces PMVEC apoptosis by targeting Wnt5a. This indicates that Wnt5a plays an important role in COPD development.

Some ncRNAs can promote COPD development by targeting the Wnt signaling pathway. Studies have shown that the lncRNA LUCAT1 is upregulated in patients with COPD. Subsequent mechanistic studies indicated that knockdown of lncRNA LUCAT1 could reverse cell apoptosis by targeting the miR-181a-5p/Wnt/ β -catenin axis.⁷⁷ In a CSE-induced mouse model, miR-130a was upregulated. Inhibition of miR-130a can rescue CSE-induced injury by targeting the Wnt signaling pathway.⁷⁸

The above findings have confirmed the interaction between Wnt signaling pathway and some nc-RNAs. Advances in bioinformatics also provide new insights into their underlying interaction mechanisms. Recent bioinformatics studies have indicated that some nc-RNAs can regulate the Wnt signaling pathway participating in COPD pathogenesis. For instance, miR-218, miR-133a/b, miR-455-3p, miR-21-3p, miR-23a, miR-25, miR-145, and miR-224 have been reported to be differentially expressed in COPD. Gene set enrichment analysis (GSEA) and/or Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis showed that nc-RNAs might strongly target the Wnt signaling pathway.^{82–84} However, there is a lack of evidence to clarify their regulatory effect on the Wnt pathway and their specific involvement in COPD development. Further studies are required to confirm these results.

Table 1 Crosstalk of Non-Coding RNA and Wnt/ β -Catenin Signaling Proteins in COPD

Non-Coding RNAs	Expression	Targeting Wnt/ β -Catenin Signaling	Reference
let-7c-3p	Downregulation	Not reported	[76]
miR-30b	Downregulation	Wnt5a	[40]
lncRNA LUCAT1	Upregulation	β -catenin, Cyclin D1, TCF4	[77]
miR-181a-5p	Downregulation	β -catenin, Cyclin D1, TCF4	[77]
miR-218	Upregulation	Wnt1	[78]

Therapeutic Strategies Targeting Nc-RNAs and Wnt Signaling Pathway in COPD

An increasing number of studies have confirmed that nc-RNAs and Wnt signaling pathways play a vital role in COPD pathogenesis. Therapeutic strategies targeting nc-RNAs and the Wnt signaling pathway may provide new insights into the treatment of COPD. Based on previous studies, a diverse array of pharmacological agents has been developed to modulate Wnt signaling.^{85–94} These pharmacological agents target different molecules in the Wnt signaling pathway. Some of the agents are listed in Table 2. Although many drugs target the Wnt signaling pathway, their use in COPD has seldom been documented. Previous studies have reported that GSK3 inhibitors can improve CS-induced lung injury and inflammation by activating the Wnt pathway.^{95–98} It should be noted that activation of the Wnt signaling pathway may lead to the development of tumors or other diseases. Therefore, side effects of pharmacological agents should also be considered, and targeting nc-RNAs may serve as a more promising therapeutic strategy.

In recent years, therapeutic strategies targeting nc-RNAs, particularly miRNAs, have attracted significant attention. High-throughput sequencing technology and bioinformatics analysis have confirmed that an increasing number of miRNAs have been identified in COPD. Targeted miRNA therapy has also demonstrated efficacy. For instance, miR-3202, miR-145-5p, and miR-181c are downregulated in COPD, and upregulation of these miRNAs could improve COPD development via anti-inflammatory and anti-apoptosis.^{99–101} In addition, miR-206 and miR-27-3p are upregulated in COPD, and downregulation of these miRNAs improves COPD development via anti-inflammatory and anti-apoptotic effects.^{61,102} However, these therapeutic strategies remain at the stage of animal and cell experiments, and remain a significant challenge for clinical applications.

Challenges and Future Directions of Nc-RNAs and Wnt Signaling Pathway in COPD

Although the roles of the Wnt signaling pathway and nc-RNAs in COPD have been extensively studied, some challenges remain. First, the role of the Wnt signaling pathway in COPD remains to be investigated. Some studies suggest that inhibition of the Wnt signaling pathway is a key mechanism in COPD, whereas other studies indicate that its activation may promote airway remodeling.^{30–32} These differences may be related to the choice of subjects, severity of COPD, and different detection methods. Second, the mechanism of the Wnt signaling pathway in COPD remains controversial. Some studies have suggested that activation of the Wnt signaling pathway may suppress inflammatory responses and apoptosis in COPD, whereas other studies have demonstrated that activation of this pathway can promote airway remodeling in COPD.^{30,36,46} The inconsistent research conclusions may be attributed to multiple confounding factors. First, the activation level and duration of Wnt signaling vary significantly across different stages of COPD. Wnt signaling exerts a protective effect in the early compensatory repair stage of lung injury, while persistent overactivation in the advanced stage promotes pathological remodeling of lung tissue. Second, the functional differences of Wnt signaling are cell-type

Table 2 Pharmacological Agents Target Wnt Signaling Pathway

Compound	Target	Function	Wnt Inhibition/Activation	Reference
OMP-18R5	Frizzled	Against FZD receptors	Inhibition	[85,86]
OMP-54F28	FZD	FZD8 decoy receptor	Inhibition	[87,88]
LGK974	PORCN	PORCN inhibitors	Inhibition	[89,90]
Pyrvinium	CK1 α	CK1 α activators but inhibit Wnt	Inhibition	[91,92]
ICG-001	CBP	Inhibits CBP/ β -catenin complex	Inhibition	[93]
PRI-724	CBP	Inhibits CBP/ β -catenin complex	Inhibition	[93]
ETC-159	PORCN	PORCN inhibitors	Inhibition	[94]
Lithium	GSK3	Inhibits GSK3 but activates Wnt	Activation	[95]
TDZD8	GSK3	Inhibits GSK3 but activates Wnt	Activation	[96]
SB216763	GSK3	Inhibits GSK3 but activates Wnt	Activation	[97]
CHIR 99021	GSK3	Inhibits GSK3 but activates Wnt	Activation	[98]

specific. Wnt pathway activation plays distinct roles in alveolar epithelial cells, airway smooth muscle cells and inflammatory immune cells, leading to opposite biological effects. In addition, differences in animal models, intervention methods, and detection indicators in existing studies also contribute to conflicting experimental results. Despite the current progress, there remain considerable knowledge gaps in clarifying the ncRNA-Wnt regulatory network in COPD. The specific upstream and downstream regulatory mechanisms of different ncRNA subtypes targeting the Wnt pathway in COPD progression have not been fully elucidated. Moreover, the dynamic changes and precise threshold of Wnt signaling activation mediated by ncRNAs at different disease stages remain unclear. Further studies are required to resolve existing controversies, clarify the spatiotemporal regulatory pattern of the ncRNA-Wnt axis, and provide more accurate and targeted theoretical basis for the clinical treatment of COPD. The resolution of these points depends on multi-center, large-sample clinical studies and rigorous experimental design.

Emerging technologies, such as artificial intelligence (AI), machine learning, single-cell RNA sequencing, spatial transcriptomics, CRISPR-Cas9 technology, and synthetic biology, have provided new directions for the study of ncRNAs and Wnt signaling pathways in COPD. AI can be utilized for predicting the regulatory networks of ncRNA and Wnt pathways, machine learning can be employed for screening biomarkers of COPD, single-cell RNA sequencing can reveal changes in the Wnt signaling pathway and nc-RNA expression across different cell types in the lung tissue of COPD patients, spatial transcriptomics can elucidate the spatial distribution of the Wnt signaling pathway and nc-RNAs in lung tissue, CRISPR-Cas9 technology can be utilized for functional validation of ncRNA, and synthetic biology can be utilized in the design of ncRNA-targeted therapies. Additionally, exosomes, as carriers of ncRNAs, deserve attention for their potential applications in COPD treatment.^{103–107} Additionally, integrated multi-omics analyses, such as a combination of genomics, transcriptomics, proteomics, and metabolomics, can comprehensively elucidate the regulatory networks of ncRNAs and Wnt pathways in COPD. The advancement of these research directions is expected to drive breakthroughs in the study of ncRNAs and Wnt pathways, thereby providing novel strategies for the precise diagnosis and treatment of COPD.

Conclusion

In summary, the Wnt signaling pathway acts as a core regulatory axis participating in the entire pathological process of COPD, including airway inflammation, airway remodeling, and apoptosis. Aberrant activation or inhibition of Wnt signaling exerts dual, stage-dependent biological effects on COPD progression, which explains the inconsistent research conclusions in current studies. As critical regulatory molecules, nc-RNAs including miRNAs, lncRNAs, and circRNAs can precisely modulate the activation status of the Wnt pathway by targeting its key molecules, thereby mediating the occurrence and development of COPD. The interactive regulatory network between nc-RNAs and Wnt signaling provides a novel molecular mechanism for exploring the pathological basis of COPD.

Data Sharing Statement

All data generated or analyzed in this study are included in this published article.

Acknowledgment

We acknowledge the Figdraw (www.figdraw.com) as the figures were drawn by Figdraw.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research received no external funding.

Disclosure

The authors declare no conflicts of interest in this work.

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