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Minireviews

Perspectives on Wnt Signal Pathway in the Pathogenesis and Therapeutics of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease with progressive airflow limitation and functional decline. The pathogenic mechanisms for this disease include oxidative stress, inflammatory responses, disturbed protease/antiprotease equilibrium, apoptosis/proliferation imbalance, senescence, autophagy, metabolic reprogramming, and mitochondrial dysfunction. The Wnt signaling pathway is an evolutionarily conserved signaling pathway that is abnormal in COPD, including chronic bronchitis and pulmonary emphysema. Furthermore, Wnt signaling has been shown to modulate aforementioned cellular processes involved in COPD. From this perspective, we provide an updated understanding of the crosstalk between Wnt signal and these cellular processes, and highlight the crucial role of the Wnt signal during the development of COPD. We also discuss the potential for targeting the Wnt signal in future translational and pharmacological therapeutics aimed at prevention and treatment of this disease.

Introduction

Chronic obstructive pulmonary disease (COPD), a preventable and treatable disease of respiratory system, is characterized by irreversible airflow obstruction and loss of functional pulmonary tissue (Cabrera López et al., 2018). The main risk factor for COPD is the exposure to tobacco smoking. Other types of inhalations also contribute to the risk of developing COPD, such as toxic particles and gases in biofuels and air pollution. COPD will become the third ranked cause of death by 2020 (Cabrera López et al., 2018). Currently, effective treatments are limited to halting or reversing the progression of this disease. Therefore, understanding the molecular mechanisms underlying lung injury and repair processes would provide potential targets and strategies for intervening in the progression of COPD.

Accumulating evidence shows that the Wnt signal pathway is abnormal during the development of COPD (Wang et al., 2011; Heijink et al., 2013; Baarsma et al., 2017; Skronska-Wasek et al., 2017). In general, the Wnt canonical pathway is downregulated, whereas noncanonical signaling is upregulated in COPD. In this review, we discuss the role of the Wnt signal in the pathogenesis of COPD and potential therapeutics for this disease that target the Wnt signal pathway.

Cellular Processes in the Pathogenesis of COPD

It is well known that oxidative stress, inflammatory responses, protease/antiprotease imbalance, and disturbed apoptosis/proliferation equilibrium are important contributors to the pathogenesis of COPD (Yao and Rahman, 2011). To date, much research has focused on the roles of senescence, autophagy, metabolism, and mitochondrial dysfunction in the development of COPD (Yue and Yao, 2016; Zhao et al., 2018). Nevertheless, further investigations are needed to determine whether potential therapeutics can be developed for this disease with these cellular processes as a basis.

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ABBREVIATIONS: AMPK, AMP-activated protein kinase; APC, adenomatous polyposis coli; CBP, CREB binding protein; CK1α, casein kinase 1 α; COPD, chronic obstructive pulmonary disease; DAG, diacylglycerol; Dsh/Dvl, dishevelled; FZD, Frizzled; GSK3, glycogen synthase kinase 3; IL, interleukin; IP3, inositol 1,4,5-trisphosphate; JNK, c-Jun-N-terminal kinase; LEF, lymphoid enhancer-binding factor; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; PCP, planar cell polarity; ROS, reactive oxygen species; SFRP, secreted frizzled-related protein; TCF, T cell-specific transcription factor; TLR, Toll-like receptor.

Wnt Pathway and Regulation

Canonical and Noncanonical Wnt Signal Pathway. The first Wnt gene, i.e., mouse Wnt1, was discovered in 1982 as a proto-oncogene in mammary tumors (Nusse and Varmus, 1982). Wnt signals comprise a family of signaling molecules that control a variety of developmental and physiologic processes (Willert and Nusse, 2012). Wnt signaling has been grouped into canonical (β-catenin-dependent) and noncanonical (β-catenin-independent) signaling pathways (Fig. 1). There are at least 19 Wnt ligands that trigger specific and distinct Wnt pathways. In general, Wnt1, Wnt2, Wnt3A, Wnt8, and Wnt10B induce the canonical Wnt pathway, with Wnt3A the most studied ligand. In contrast, Wnt5A is the broadly studied ligand for the noncanonical Wnt signal, although Wnt4 and Wnt11 also mediate this pathway (Baarsma et al., 2013). Nevertheless, Wnt ligands are not intrinsically canonical or noncanonical, as some Wnt ligands are able to activate multiple signaling pathways.

Wnt canonical signaling is dependent on a transcription coactivator, β-catenin, which is initiated by the binding of Wnt ligands to their receptors, including a member of the Frizzled (FZD) family of serpentine receptors and the coreceptor LRP 5/6 (MacDonald and He, 2012; Baarsma and Konigshoff, 2017). This leads to the recruitment of the destruction complex to the plasma membrane and the inhibition of glycogen synthase kinase 3 (GSK3). GSK-3 is recognized as a dual-specificity kinase regulated by tyrosine and serine/threonine phosphorylation (Tejeda-Muñoz and Robles-Flores, 2015). There are two different genes that encode for GSK-3 isoforms (GSK-3α and GSK-3β) (Woodgett, 1990; Shaw et al., 1998). Both isoforms function redundantly in the destruction complex (Doble et al., 2007). GSK3 inhibition results in reduced phosphorylation and degradation of β-catenin, which enhances the translocation and accumulation of β-catenin into the nucleus, where β-catenin binds to the members of the T cell-specific transcription factor/lymphoid enhancer-binding factor (TCF/LEF) family, leading to transcription of targeting genes (Langton et al., 2016; Muneer, 2017; Naspi et al., 2017; Skronska-Wasek et al., 2018). In the condition of reduced Wnt signal, β-catenin is phosphorylated and degraded via a proteasome-dependent process by the β-catenin destruction complex, which includes the scaffold proteins Axin and adenomatous polyposis coli (APC), the Ser/Thr kinases casein kinase 1, protein phosphatase 2A, and GSK3 (Taelman et al., 2010; Kaidanovich-Beilin and Woodgett, 2011; van Kappel and Maurice, 2017). Axin phosphorylation in both Wnt-off and Wnt-on states requires the tumor suppressor APC in *Drosophila*, suggesting a more active and multifaceted role for APC in Wnt signaling (Tacchelly-Benites et al., 2018).

The most studied noncanonical pathway is the planar cell polarity (PCP) pathway acting via c-Jun-N-terminal kinase (JNK) and the Wnt-Ca^{2+}, Ca^{2+}-dependent signal. Although activation of noncanonical Wnt signaling also requires the binding of specific Wnt ligands (e.g., Wnt-4 or Wnt-5A) to FZD receptors, it seems to be independent of LPR5/6 coreceptors. Wnt5A-dependent noncanonical Wnt signaling has been shown to inhibit Wnt3A-induced Wnt/β-catenin signaling (Bryja et al., 2007), suggesting that the PCP and Wnt/β-catenin signaling can antagonize each other.

Regulation of β-Catenin Phosphorylation. In addition to GSK3β, other kinases can also phosphorylate β-catenin. AKT can directly phosphorylate β-catenin at serine 552 but increases its cytoplasmic and nuclear accumulation (Fang et al., 2007). Protein kinase A activation leads to β-catenin

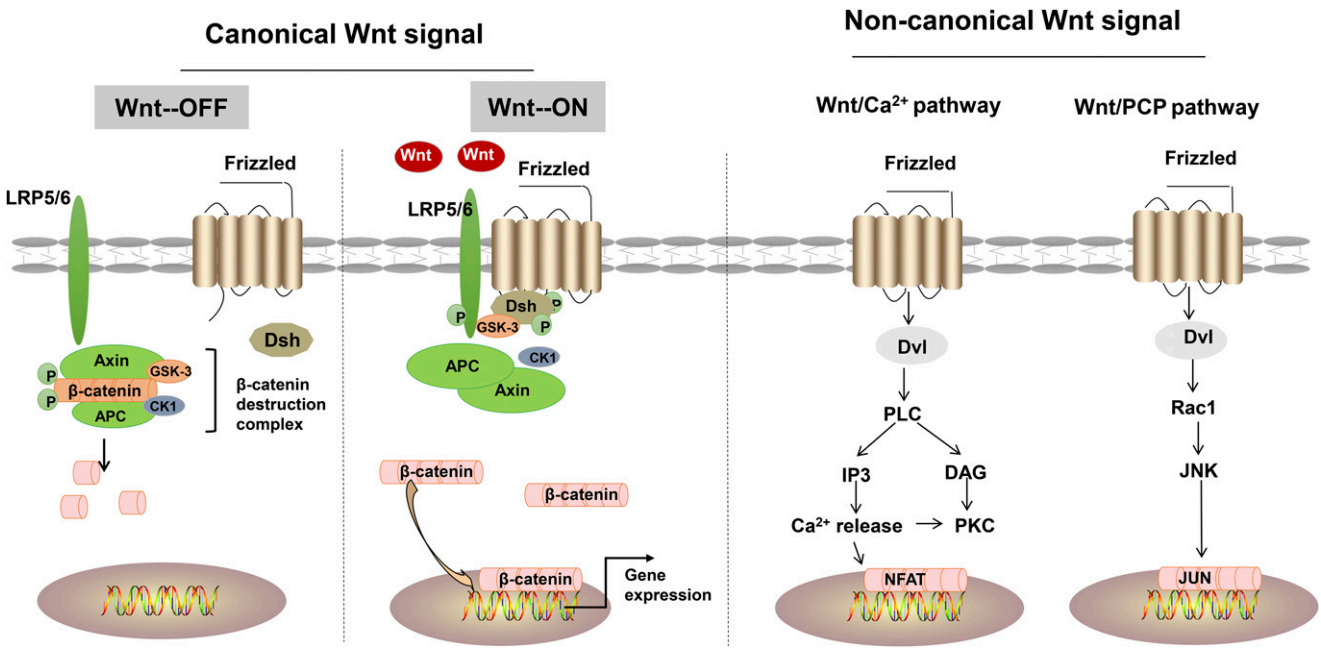

Fig. 1. Switch-on and switch-off of canonical and noncanonical Wnt signal pathway. During canonical Wnt pathway, in the absence of Wnt ligand, β-catenin is phosphorylated and degraded by a destruction complex that includes the scaffold proteins Axin and adenomatous polyposis (APC), the Ser/Thr kinases casein kinase 1 and glycogen synthase kinase 3 (GSK3). Upon Wnt activation, β-catenin translocates to the nucleus and then associates with TCF/LEF family transcription factors to activate target gene expression. The two noncanonical pathways are Wnt/calcium and PCP pathways. For Wnt/calcium pathway, Wnt stimulates calcium release, activating PLC and subsequent the transcription factor NFAT. The Wnt/PCP pathway is mediated by the activation of JNK. Dsh/Dvl: dishevelled; PLC: phospholipase C; IP3: inositol 1,4,5-triphosphate-3; DAG: diacylglycerol; NFAT: nuclear factor of activated T cells.

phosphorylation at Y654 and S675, which also promotes nuclear translocation of β-catenin (Liu and Habener, 2008; Bellei et al., 2011; Law et al., 2013). There is a functional cooperation between JNK and β-catenin (Nateri et al., 2005; Lee et al., 2009). Activated JNK promotes β-catenin degradation, which is associated with increased β-catenin phosphorylation at ser33 and ser37 residues by GSK3β (Hu et al., 2009). This is corroborated by the finding that high levels of nuclear JNK activity in early *Xenopus* embryos blocked nuclear accumulation of β-catenin (Liao et al., 2006). AMP-activated protein kinase (AMPK) enhances β-catenin phosphorylation at Ser33, Ser37, and Thr41 residues and promotes the protein degradation of β-catenin by GSK3β in Saos-2 cells (Takatani et al., 2011). On the contrary, AMPK phosphorylates β-catenin at Ser552, which stabilizes β-catenin and enhances β-catenin/TCF-mediated transcription in rat mesenchymal cells (Zhao et al., 2010). These findings suggest that the β-catenin phosphorylation on its stability is residue-specific.

Wnt Pathway in COPD

Previous studies have shown that adult lung tissues express a variety of Wnt ligands (e.g., Wnt3, Wnt4, Wnt5a, Wnt7a, Wnt7b, Wnt10b, and Wnt 11), receptors (e.g., FZD3, FZD6, and FZD7), and signal components (e.g., Dvl and Dickkopf). In general, β-catenin, TCF, and Frizzled-4 are reduced in patients with pulmonary emphysema compared with normal donors (Wang et al., 2011; Skronska-Wasek et al., 2017). In contrast, Wnt4, Wnt5a, Wnt5b, and Wnt10b are increased in patients with pulmonary emphysema (Heijink et al., 2013, 2016; Baarsma et al., 2017) (Table 1). Interestingly, secreted frizzled-related protein 1 (SFRP1), a Wnt inhibitor, is increased in lung tissues from patients with pulmonary emphysema, whereas Frizzled-8 is upregulated in patients with chronic bronchitis (Foronjy et al., 2010; Wang et al., 2011) (Table 1).

Wnt/β-catenin activation by lithium chloride attenuates airspace enlargement and lung function decline in mice with pulmonary emphysema, whereas Wnt-5a overexpression in lung type II cells aggravated airspace enlargement in elastase-induced pulmonary emphysema in mice (Kneidinger et al., 2011; Baarsma et al., 2017; Cui et al., 2018). The mechanisms are associated with the regulation of cellular processes involved in COPD as we discuss below (Fig. 2).

Oxidative Stress. Exogenous and endogenous generation of reactive oxygen species (ROS) has been shown to cause lung injury and subsequent COPD. Increased oxidative stress is also attributable to a reduced antioxidant system, including Nrf2, HO-1, superoxide dismutase (SOD), and glutathione, during the development of COPD.

It has been shown that H_2O_2 induces dephosphorylation and stabilization of β-catenin (Funato et al., 2006; Kajla et al., 2012), suggesting the link between oxidative stress and the Wnt/β-catenin pathway. Treatment with antioxidant *N*-acetyl cysteine suppresses Wnt3a-induced dephosphorylation of β-catenin in endothelial cells (Vikram et al., 2014). This may have been the result of reduced NADPH oxidase-4-derived ROS by *N*-acetyl cysteine in response to Wnt3a treatment. Further study showed that mitochondrial ROS promoted the dissociation of Dishevelled from its complex with nucleoredoxin, which augments Wnt/β-catenin signaling efficiency (Rharass et al., 2014). This was also corroborated by findings that SOD3 knockdown in mice activated Wnt2/β-catenin signaling (Thimraj et al., 2017). Nrf2 also has the ability to inhibit Wnt/β-catenin pathway (Manigandan et al., 2015), which is associated with the direct interaction between β-catenin N-terminus and β-TrCP1, an antagonist of both Nrf2 and β-catenin (Long et al., 2017).

Constitutively active β-catenin expression in the endothelium increased vascular ROS and impaired endothelium-dependent vasorelaxation (Vikram et al., 2014). We have shown that Wnt3a/β-catenin pathway activation increases Nrf2 and HO-1 levels in bronchial epithelial cells after cigarette smoke exposure, and protects against pulmonary emphysema induced by elastase in mice (Cui et al., 2018). Both Wnt and Nrf2 are reduced in retinal pigment epithelial cells when mice are exposed to chronic cigarette smoke, which is associated with GSK3β phosphorylation (Ebrahimi et al., 2018). In addition to β-catenin, Gsk3β activation via p-Gsk3β (tyr216) is able to phosphorylate Nrf2 leading to Nrf2 degradation independent of a kelch-like ECH-associated protein 1 pathway (Rada et al., 2011). This is in agreement with findings that Wnt3a regulates an Axin1/Nrf2 complex in hepatocytes (Rada et al., 2015). All these findings suggest a bidirectional feedback loop between Wnt and Nrf2 through phosphorylated GSK3β. The different regulation between Nrf2 and Wnt may also be owing to different cell types. Overall, targeting the Wnt/β-catenin pathway and oxidative stress would be a promising strategy to attenuate the lung damage in COPD.

Inflammation. Abnormal inflammatory responses are observed in patients with COPD. This is the result of increased infiltration of inflammatory cells as well as release of proinflammatory mediators. Increased inflammatory response

TABLE 1
The changes of Wnt signal molecules in patients with chronic bronchitis and pulmonary emphysema

Disease	Molecule	Change	Reference
Chronic bronchitis	Frizzled-8	Increase in bronchial epithelial cells	Spanjer et al., 2016
Pulmonary emphysema	SFRP1	Increase in lung homogenates	Foronjy et al., 2010
COPD	Wnt4	Increase in bronchial epithelial cells, stromal cells	Durham et al., 2013; Heijink et al., 2013
	Wnt5a	Increase in lung homogenates and oncosomes	van Dijk et al., 2016; Feller et al., 2018
	Wnt5b	Increase in bronchial epithelial cells	Heijink et al., 2016
	Wnt10b	Increase in lung homogenates	Kneidinger et al., 2011
	β-catenin	Decrease in small-airway epithelium and lung homogenates; reduction in nuclear β-catenin-positive alveolar epithelial cells	Kneidinger et al., 2011; Wang et al., 2011; Baarsma et al., 2017
	Frizzled-4	Decrease in alveolar epithelial cells	Skronska-Wasek et al., 2017
	TCF7L1	Decrease in lung homogenates	Wang et al., 2011
	SFRP2	Increase in small airway epithelium and lung homogenates	Wang et al., 2011; Baarsma et al., 2017

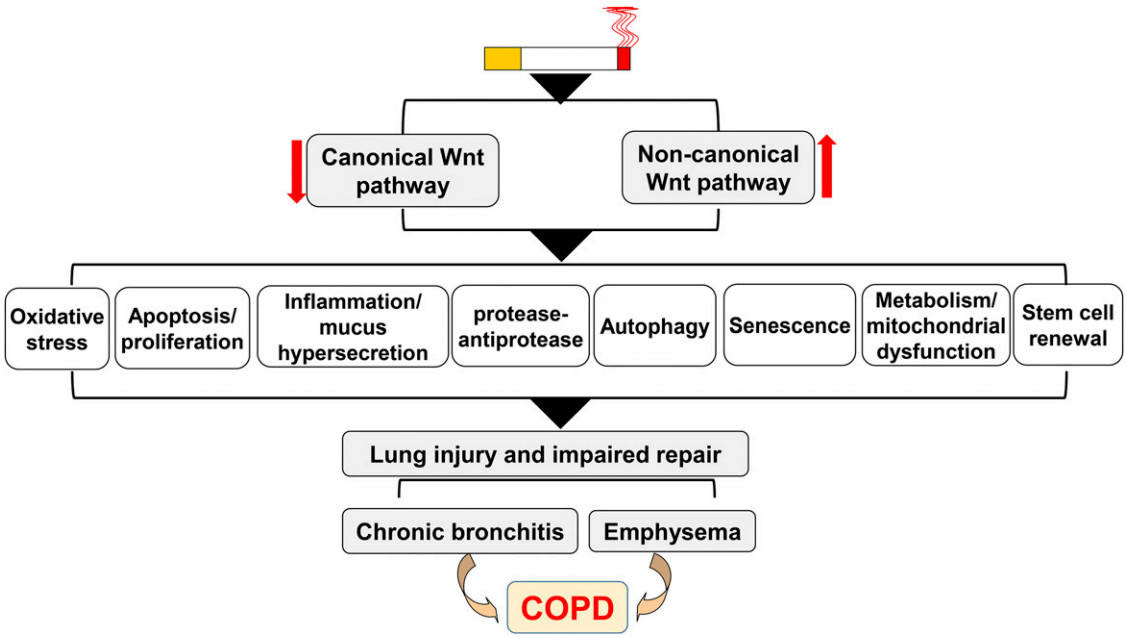

Fig. 2. Regulation of Wnt signal in the development of COPD/emphysema. Cigarette smoke exposure causes the dysregulation of canonical and noncanonical Wnt signal pathways, which results in the alteration of oxidative stress, apoptosis/proliferation, inflammation, mucus hypersecretion, protease/antiprotease imbalance, autophagy, senescence, metabolism reprograming, mitochondrial dysfunction, or stem-cell/progenitor-cell renewal. All of these cellular processes participate in the pathogenesis of chronic bronchitis or pulmonary emphysema through increased lung injury and impaired lung repair.

could lead to irreversible and progressive airflow limitation and lung function decline (Barnes, 2016). The mechanisms underlying abnormal inflammatory response are associated with activation of Toll-like receptor (TLR), mitogen-activated protein kinase (MAPK), protein kinase A, and nuclear factor (NF)-κB signal pathways.

Lipopolysaccharide-induced acute lung injury is associated with suppression of Wnt/β-catenin pathway (Suo et al., 2018). Enhancing Wnt signaling is capable of attenuating TLR signaling and mediating the inflammatory response in lung alveolar epithelial cells (Li et al., 2014). In macrophages, Wnt5a induces inflammatory response via FZD5, whereas Wnt3a, a ligand of FZD1, mediates anti-inflammatory effects on mycobacteria-infected macrophages via the Wnt/β-catenin signaling pathway by regulating the TLR/NF-κB pathway (Schaale et al., 2011). Treatment with recombinant Wnt5a or Wnt5b increased interleukin (IL)-6 and IL-8 release, which is higher in lung fibroblasts from COPD patients than non-COPD controls (van Dijk et al., 2016). Likewise, the noncanonical Wnt pathway activation by Wnt4 increases IL-8, IL-6, RANTES (regulated on activation normal T cell-expressed and secreted), and monocyte chemotactic protein-1 in bronchial epithelial cells (Heijink et al., 2013). This is associated with activation of p38 and JNK-MAPK pathways, leading to neutrophil infiltration and inflammation in COPD (Durham et al., 2013). This is in agreement with the finding that the proinflammatory role for the FZD-8 receptor in mucus hypersecretion by increasing MUC5AC expression during chronic bronchitis (Spanjer et al., 2016). In contrast, cigarette smoke exposure reduces the activity of Wnt/β-catenin signaling in both bronchial epithelial cells and mice. Treatment with β-catenin activator SB216763 significantly reduces cigarette smoke extract–induced secretion of the inflammatory cytokines tumor necrosis factor α and IL-1β in bronchial epithelial cells by modulating peroxisome proliferator-activated receptor δ and the p38 MAPK pathway (Guo et al., 2016). Further study is required to determine how canonical and noncanonical Wnt signal pathways differentially modulate MAPK-dependent inflammatory responses and whether this is cell-specific.

Matrix Metalloproteinases. Imbalance of matrix metalloproteinases (MMP)/tissue inhibitor of metalloproteinases toward increased MMPs is thought to contribute to the destruction of alveoli, resulting in emphysema (Stockley et al., 2013). Findings from human disease and experimental models suggest that MMP-7, MMP-9, MMP-10, MMP-12, and MMP-28 participate in the development of COPD (Skjot-Arkil et al., 2012; Kaur et al., 2016). Both MMP-2 and MMP-9 promoters contain LEF/TCF binding sites, and Wnt activation through FZD receptor induces MMP-2 and MMP-9 gene expression in T cells (Wu et al., 2007). SFRPs can bind soluble Wnt and inhibit Wnt's interaction with FZD receptors, which antagonizes their action. SFRP1 and SFRP2 are upregulated in lung tissues of patients with pulmonary emphysema, which is associated with increased MMP-1 and MMP-9 levels (Foronjy et al., 2010; Wang et al., 2011). Although SFRP2 is specifically upregulated in the ciliated epithelial cells from healthy smokers and smokers with COPD (Wang et al., 2011), Heijink et al. (2013) were not able to detect SFRP2 expression in the epithelial cell lines. This difference could be owing to different factors present in the epithelial microenvironment (Heijink et al., 2013). Wnt5B increases levels of MMP-2 and MMP-9 in human bronchial epithelium (Heijink et al., 2016). However, exogenously added Wnt4 does not affect the genes of MMP2 and MMP9 in human bronchial epithelium after cigarette smoke exposure (Heijink et al., 2013). These findings suggest that Wnt signal regulates MMP expression in a ligand-specific manner.

Apoptosis/Proliferation. Apoptosis of lung structural cells, including epithelial cells, endothelial cells, and fibroblasts,

contributes to the process of lung damage in COPD. This is imbalanced by reduced proliferation leading to impaired repair after lung injury. Reduced or delayed apoptosis of neutrophils is observed in COPD (Hoenderdos and Condliffe, 2013), leading to increased inflammatory responses.

FZD4 is reduced in type II cells in patients with COPD compared with nonsmokers or smokers. Overexpression of FZD4 activates the Wnt/β-catenin pathway, and promotes type II cell proliferation and transdifferentiation into type I cells (Skronska-Wasek et al., 2017). This is corroborated by the findings that single-cell Wnt signaling niches maintain stemness of alveolar type II cells (Nabhan et al., 2018). This provides a potential therapeutic avenue for replenishment of alveolar type II cells by maintenance of canonical Wnt signal in COPD. Furthermore, treatment of MRC-5 fibroblast using basic fibroblast growth factor, a well known proliferation inducer in COPD, enhanced Wnt5a and β-catenin expressions (Ge et al., 2016). These findings suggest an important role for the Wnt canonical pathway in enhancing lung repair after injury.

Senescence. Senescence occurs in patients with COPD and in mice with emphysema (Yao et al., 2012; Ahmad et al., 2015). There are a few studies investigating the link between Wnt signal and lung aging (Kneidinger et al., 2011; Hofmann et al., 2014; Kovacs et al., 2014). For instance, a decrease in canonical Wnt signaling (e.g., Wnt3a) and an increase of noncanonical pathway (e.g., Wnt5A) are observed in aged lungs. In addition, expression of Wnt pathway-related genes are altered in lung tissues of old mice. The levels of Tle1, Tef1, and Nkd1 are decreased, whereas Frzb is increased, in lungs of older mice (36 months old) compared with young mice (5 months old) (Hofmann et al., 2014). Further studies on the role of Wnt signal in lung aging/senescence during the development of COPD may uncover novel mechanisms for this disease.

Autophagy. Autophagy, including mitophagy and ciliaphagy, has been shown to modulate the development of COPD (Cloonan et al., 2014; Ahmad et al., 2015). Autophagy negatively regulates Wnt signaling by promoting Dishevelled degradation (Gao et al., 2010), whereas inhibition of Wnt/β-catenin signaling upregulates SQSTM1/p62 and sensitizes glioblastoma cells for proliferation and apoptosis to autophagy blockers (Nàger et al., 2018). Although SB216763, a selective small-molecule inhibitor of GSK3, protects against bleomycin-induced pulmonary fibrosis via activation of autophagy (Gurrieri et al., 2010), it remains elusive whether there is an interaction between autophagy and Wnt signaling during the development of COPD.

Mitochondrial Dysfunction. Mitochondrial dysfunction occurs in patients with COPD, and this includes abnormal mitochondrial biogenesis, fusion/fission, and mitophagy (Mizumura et al., 2014; Ahmad et al., 2015). Wnt signaling has been shown to regulate mitochondrial biogenesis and fusion/fission, which is cell- and organ-specific (An et al., 2010; Yoon et al., 2010; Godoy et al., 2014; Bernkopf and Behrens, 2018; Singh et al., 2018). For instance, activation of Wnt signal by Wnt3a results in an increase in mitochondria in human osteosarcoma cell. Wnt5a ligand modulates mitochondrial fission-fusion in rat hippocampal neurons. These findings suggest that the Wnt signal regulates mitochondrial function in a ligand-specific manner. Further investigation of the role of Wnt signal in cigarette smoke-induced mitochondrial dysfunction would provide novel insights into molecular mechanisms for COPD.

Metabolism. Lung epithelial cells exposed to cigarette smoking have shown a decrease in glycolysis but an increase in fatty acid oxidation, suggesting that metabolic dysregulation may regulate lung destruction and impaired repair in COPD (Agarwal et al., 2014; Jiang et al., 2017; Cruickshank-Quinn et al., 2018). Exposure of human lung fibroblast to cigarette smoke inhibits oxidative phosphorylation complex III (Lei et al., 2017). Proteomic analysis of livers from liver-specific APC knockout mice has shown dysregulated proteins involved in mitochondrial dysfunction and carbohydrate metabolism, suggesting that defects in Wnt signaling may contribute to a metabolic switch in fuel utilization toward glycolysis and away from fatty acid oxidation (Chafey et al., 2009). This is corroborated by the findings that Wnt signaling activates TP53-induced glycolysis (Liu et al., 2019). The mechanisms are associated with transcription factors FOXO1 and TIGAR, or direct target genes, including monocarboxylate transporter 1 and pyruvate dehydrogenase kinase 1 (Liu et al., 2011; Pate et al., 2014; Sprowl-Tanio et al., 2016). Nevertheless, it is not known whether Wnt regulates metabolic reprogramming in response to cigarette smoke exposure or in the development of COPD.

Stem Cell Renewal. Inadequate lung tissue repair after injury contributes to the development of COPD (Bagdonas et al., 2015). In the normal condition, lung tissue turnover is slow. However, after lung injury in COPD, lung stem cells or progenitor cells are activated to replace damaged lung tissue via lung regeneration (Kokturk et al., 2018). Wnt/β-catenin signaling is involved in regulating the stem cell in the renewal of lung epithelium (Wang et al., 2009; Sun et al., 2014), suggesting that enhancing canonical Wnt signal would promote lung repair in COPD. Interestingly, knockout β-catenin in bronchiolar epithelium did not affect maintenance and repair following naphthalene-induced airway injury, indicating that β-catenin is not necessary for maintenance or repair of bronchiolar epithelium (Zemke et al., 2009). This is corroborated by the findings that low-dose Wnt treatment enhanced stem-cell proliferation, whereas high-dose treatment inhibited the proliferation of stem cells (De Boer et al., 2004). This could be attributable to the temporal and spatial effects of Wnt signaling for regenerating epithelium or endothelium after injury. Further studies are required to explore whether and how Wnt/β-catenin signaling modulates stem-cell or progenitor-cell renewal for repairing lung tissues in COPD.

Differentiation of the alveolar type I cell lineage is an important step for the formation of distal lung saccules during the embryonic stage. Systemic activation of Wnt signaling at specific stages of lung development can partially rescue the type I cell differentiation and lung alveolarization (Wang et al., 2016). However, inhibiting Wnt/β-catenin pathway by ICG-001 compound attenuates hyperoxia-induced simplification of alveolarization in neonatal rats (Alapati et al., 2014), whereas inhibition of Wnt receptor LRP5/6 by Mesd does not improve alveolarization during hyperoxia (Alapati et al., 2013). Accumulating evidence suggests that neonatal lung injury, such as bronchopulmonary dysplasia, can evolve into COPD. Hence, it is possible that COPD develops as a result of neonatal lung injury leading to aberrant Wnt signaling and thus lung repair capacity. This requires long-term follow-up studies in infants with bronchopulmonary dysplasia.

TABLE 2
Compounds targeting Wnt signal pathway

Target	Compound	Function	Reference
Wnt	OMP-54F28 (FZD8–Fc fusion)	A decoy receptor of Wnt	Jimeno et al., 2017
Frizzled	OMP-18R5	Binds to FZD7 and inhibits Wnt	Gurney et al., 2012
CK1α	Pyrvinium	Activates CK1α but inhibits Wnt	Thorne et al., 2010
β-catenin/TCF	PKF115-584; CGP049090; iCRT3; iCRT5; iCRT14; 2,4 diamino-quinazoline series; PNU-74654; BC21	Disrupts β-catenin/TCF complex and inhibits Wnt	Sukhdeo et al., 2007; Minke et al., 2009; Gonsalves et al., 2011
DVL	NSC 668036; FJ9; 3289-8625	Binds to the Dvl PDZ domain, and inhibits Wnt	Shan et al., 2005; Grandy et al., 2009
Tankyrase 1 and 2	IWR-1; XAV939; K-756	Inhibits tankyrase and Wnt	Lu et al., 2009; Okada-Iwasaki et al., 2016
Porcupine	IWP2; LGK974	Inhibits porcupine, and Wnt	Liu et al., 2013
CBP	ICG-001; PRI-724	Inhibits CBP/β-catenin complex, and Wnt	Kimura et al., 2017
GSK3	Lithium; TDZD8; SB216763; CHIR 99021	Inhibits GSK3 but activates Wnt	Hedgepeth et al., 1997; Eldar-Finkelman and Martinez, 2011; Uhl et al., 2015

CBP: CREB-binding protein; CK1α: casein kinase 1α; Dvl: dishevelled; TCF: T-cell factor/lymphoid enhancer factor.

Pharmacologically Targeting Wnt Signal Pathway

There are numerous pharmacological compounds targeting the Wnt signal pathway. Table 2 shows the compounds and their targets in Wnt signal pathway. Except for GSK3 inhibitors activating the canonical Wnt signal, most are inhibitors of the Wnt signal pathway. These compounds are either FDA-approved or in clinical trials as tumor treatments or at preclinical stages. A few groups report using GSK3 inhibitors to activate Wnt pathway to attenuate cigarette smoke–induced lung inflammation and injury (Baarsma et al., 2011; Kneidinger et al., 2011; Guo et al., 2016; Cui et al., 2018). Their findings suggest potential therapies for preventing or treating COPD using Wnt-signal modulators. The Wnt signal plays important roles in tissue homeostasis and cancer stem-cell proliferation and renewal in multiple organs, including lung (Wang et al., 2018). Therefore, the side effects should be considered during the development of therapeutic strategies to activate the Wnt pathway for COPD.

Conclusion and Future Directions

COPD is a chronic respiratory disease characterized by loss of parenchymal alveolar tissue and impaired tissue repair. Therapeutic targets are limited. Several studies have revealed that the Wnt signaling pathway is involved in lung development, homeostasis, and the lung epithelial injury and repair process in COPD. Targeting the Wnt signal would provide novel therapeutics to intervene in the development of COPD. Yet, the molecular mechanisms underpinning the pathogenesis of Wnt signaling components in COPD, including the destructive complex, remain largely unclear. Wnt signaling is temporal, and both the activation and subsequent reduction of Wnt signaling are required for normal homeostasis or repair after injury. Thus, it is important to study the dynamics of Wnt signal during the development of COPD. β-catenin is able to bind to a variety of transcription factors other than TCF/LEF, which modulate a broad spectrum of downstream biologic processes. Therefore, it is important to determine whether any of these therapeutic agents that specifically target the Wnt pathway will be beneficial for COPD/emphysema and have an acceptable safety profile.

Authorship Contributions

Participated in research design: Gao, Yao.

Wrote or contributed to the writing of the manuscript: Qu, Yue, Gao, Yao.

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