Non-canonical WNT signalling in the lung

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The role of WNT signalling in metazoan organogenesis has been a topic of widespread interest. In the lung, while the role of canonical WNT signalling has been examined in some detail by multiple studies, the non-canonical WNT signalling has received limited attention. Reliable evidence shows that this important signalling mechanism constitutes a major regulatory pathway in lung development. In addition, accumulating evidence has also shown that the non-canonical WNT pathway is critical for maintaining lung homeostasis and that aberrant activation of this pathway may underlie several debilitating lung diseases. Functional analyses have further revealed that the non-canonical WNT pathway regulates multiple cellular activities in the lung that are dependent on the specific cellular context. In most cell types, non-canonical WNT signalling regulates canonical WNT activity, which is also critical for many aspects of lung biology. This review will summarize what is currently known about the role of non-canonical WNT signalling in lung development, homeostasis and pathogenesis of disease.

Keywords: development/lung/non-canonical/WNT.

WNT signalling is critical to many cellular activities including proliferation, differentiation, migration, cell polarity, cell adhesion and cell fate specification (1, 2). WNT activates several intracellular pathways including the β-catenin-dependent ‘canonical’ pathway, and the ‘non-canonical’, β-catenin-independent pathways. The functions of canonical WNT signalling in lung development or pathologies have been extensively studied and reviewed previously (3, 4). In contrast, characterization of non-canonical WNT ligands, receptors and their cognate functions in the lung have not been adequately addressed. This study attempts to address this gap in our knowledge by reviewing and integrating relevant and reliable information that pertains to the role and mechanism of action of the non-canonical signalling pathway in the lung.

Lung Structure and Morphogenesis

The structure of the vertebrate lungs has specifically evolved to maximize efficient gas exchange between carbon dioxide that is the byproduct of cellular respiration, and oxygen from the atmosphere. Fresh air enters the lungs through trachea, mainstem bronchi and the intralobular conducting airways that include the bronchi (the larger airways) and bronchioles (smaller airways) to reach the gas exchange units, known as alveoli. These conduits are lined by multiple bronchial epithelial cell (BEC) types and are wrapped by sheets of elastic tissues and smooth muscle cells (SMCs) (Fig. 1). Major airway epithelial populations include ciliated cells, Club cells (previously named Clara cells), goblet cells, basal cells and neuroendocrine cells (NEC), each of which plays distinct functions in the lung (6). It now appears that multiple subpopulations of lung epithelial cells have the capacity to serve stem cell functions during normal maintenance or regeneration of the injured lung (7, 8). In the distal lung, there are two major populations of alveolar epithelial cells (AECs). The alveoli are covered with a layer of squamous epithelial cells, named type 1 AECs (AT1) (Fig. 1). Alveoli also include cuboidal epithelial cells which produce surfactant proteins and secrete lamellar bodies. These are the type 2 AECs (AT2), which also serve as progenitors of AT1 cells in maintaining homeostasis and also in repair of injury (9–11). AT1 cells are juxtaposed to endothelial cells that form a capillary network, in which the red blood cells take in oxygen from, and release carbon dioxide into the alveolar space. In the alveolar septal wall, multiple stromal cells exist, amongst which the most studied are lipofibroblasts, pericyte-like-cells and alveolar myofibroblast cells (AMFs). The lipofibroblasts are an important source of triglyceride for the synthesis of surfactant phospholipids (12). A recent study indicates that lipofibroblasts serve as a major component of the stem cell niche microenvironment for AT2 cells (10). Pericyte-like-cells (NG2+PDGFRA+DESMIN+) are present in the alveolar interstitium, and have been shown to contribute to formation of pulmonary fibrosis (9, 13). Alveolar myofibroblasts are contractile fibroblasts which express Acta2. AMFs in the adult lung are mainly observed around alveolar ducts (14). In
neonatal lungs which are undergoing alveogenesis, large numbers of AMFs are present in the primary septae and the tips of secondary septae of growing alveoli. These cells are essential for proper alveogenesis.

Lung organogenesis has been described in many excellent previous reviews (6, 15, 16). In brief, lung development starts around 5 weeks of gestation in human and 9.5 days (E9.5) in mouse embryos. It includes four major stages: the pseudoglandular stage (5–16 weeks of gestation in human, E9.5–E16.5 in mouse), the canalicular stage (16–26 weeks of gestation in human, E16.5–E17.5 in mouse), the saccular stage (26–36 weeks of gestation in human, E17.5–postnatal day 5 (PN5) in mouse) and the alveolar stage which lasts from 36 weeks of gestation to early postnatal age in human and from PN5 to PN30 in mouse. During the pseudoglandular stage, the epithelial airways grow and undergo repeated branching into the surrounding mesenchyme to form the proximal architecture of the lung. This is accompanied by the growth of pulmonary blood vessels. Both the conducting airways and the blood vessels are covered with SMCs, named airway smooth muscle and vascular SMCs, respectively. Several populations of airway epithelial cells including NEC and ciliated cells begin to differentiate during this stage. Cell fate of lipofibroblasts and AMF appears to be specified also in this period (5, 12, 17). During the canalicular stage, the distal airways undergo extensive branching to increase the number of distal structures, which give rise to alveolar saccules. This is accompanied by extensive growth of the capillary network in...
the surrounding mesenchyme. In this period, differentiation of bipotent alveolar epithelial progenitor cells is commenced at distal lung (11). In addition, Club cells, which are positive for SCGB1A1 (also named CCSP or CC10), also become detectable in the proximal airways. The saccular stage is considered the onset of lung maturation. Preterm neonates delivered before the onset of the saccular stage are at risk for pathogenesis of chronic lung disease known as bronchopulmonary dysplasia (BPD). During the saccular stage, the distal tips of the epithelial airways expand and the septal walls gradually become thinner. Epithelial cells lining the saccules now comprise both cuboidal (AT2) and squamous (AT1) populations. Basal cells which are TRP63+/KRT5+/KRT14+ become mature in the tracheobronchial region (18). AMF progenitors undergo dynamic changes to express Pdgfα and become scattered through the lung parenchyma (19, 20). Positioning of the AMF progenitors may specify the initiation site of the secondary septum as AMFs are thought to be the major cell type that drives the formation of secondary septae during alveogenesis. During the alveolar stage, the number of alveoli increases dramatically by formation of secondary septae, which results in increased alveolar surface area. The alveolar septae become thinner possibly through apoptosis to allow more efficient air-exchange. Patterning of the endothelial network changes dynamically in the alveolar septae to allow closer association or coupling between AT1 cells and the capillary network. Also, the AMF population reaches a peak to facilitate secondary septae formation. The developing process during the saccular and alveolar stages is essential for formation of fully functional mature lungs, and has thus been named lung maturation. Defects in lung maturation cause severe lung diseases such as BPD.

**WNT Signalling**

WNT is a large family of Cysteine-rich signalling molecules that are vertebrate homologues of Drosophila wingless. There are at least 19 WNTs identified in mammals (21). Receptors of WNT ligands include members of seven-pass transmembrane proteins Frizzleds (FZD1–10), LRP co-receptors (LRP5/6) and tyrosine kinase receptors of ROR and RYK families. Depending on the different combinations of WNT ligands and the receptors, WNT signalling activates several different intracellular pathways (22, 23). The canonical WNT pathway is mediated by stabilization of β-catenin. In the absence of WNT ligands, β-catenin is phosphorylated on Ser33, 37, 45 and Thr41 by glycogen synthase kinase 3β (GSK3β) and CKlα in a complex of APC/AXIN/GSK3β. The phosphorylated β-catenin is ubiquitinated and degraded through E3 ubiquitin ligase (24). When WNT ligands bind to their receptors FZD and co-receptors LRP5/6, they trigger intracellular responses that lead to inhibition of β-catenin phosphorylation. The stabilized β-catenin thus accumulates and translocates to the nucleus where it interacts with the LEF/TCF transcription factor complex to regulate target gene expression (25, 26).

Canonical WNT signalling controls many essential cellular activities including cell proliferation, differentiation, cell fate specification and stem cell renewal. Functional importance of canonical WNT signalling in lung morphogenesis has been analysed by different approaches and has been reviewed previously (3, 4) and will not be included in the current review.

Several WNT ligands including WNT4, WNT5a, WNT7a, WNT11 and WNT16 have been shown to activate the β-catenin-independent, non-canonical WNT pathways (27–29). Amongst these, WNT5a is the most extensively studied (30, 31). Even though it usually triggers non-canonical WNT signalling, WNT5a is also able to activate canonical WNT signalling under certain conditions (32–34). Non-canonical WNT signalling includes the WNT/PCP (planar cell polarity) and WNT/Ca²⁺ pathways (Fig. 2). The WNT/PCP pathway activates JNK and Rho-kinase cascades. The WNT/Ca²⁺ pathway increases intracellular calcium concentration and activates protein kinase C (PKC), calcineurin or CaMKII cascades. As knowledge of non-canonical WNT signalling has increased, it has become clear that this signalling network may be more complex than what had been previously thought (Fig. 2) (38–42). Recently, a novel non-canonical WNT pathway mediated by FYN tyrosine kinase and STAT3 transcriptional regulator was identified in tumour cells (35). Several studies have shown that non-canonical WNT signalling may repress canonical WNT activity. These may be mediated through different mechanisms involving CaMKII-TAK1-NLK, PKCζ, calcineurin-NFAT or Siah2 E3 ubiquitin ligase (43–46). There are a limited number of reports that show positive regulation of canonical WNT activity by non-canonical WNT signalling mediators such as Rac1 (47, 48). Non-canonical WNT signalling plays important roles in cell migration, cell polarity and stem cell maintenance. Its functions in the lung have been explored recently and will be summarized in the current review.

**Non-canonical WNT Signalling in Lung Development**

The role of non-canonical WNT signalling in lung development was studied by characterization of Wnts5a knockout lungs, generated by inserting a neomycin-resistance gene construct into exon2 of the Wnts5a gene (49, 50). Germline deletion of Wnts5a resulted in truncation of the trachea and overexpansion of the distal airways. Most importantly, lung maturation was attenuated and the mutant lungs exhibited thickened septal walls due to increased cellularity. Further analysis revealed reduced differentiation of alveolar type 1 (AT1) cells (51). To address the function of Wnt5a specifically in the lung, we also generated a Wnt5a gain-of-function model with Wnt5a overexpression specifically in lung epithelial cells through the activity of the surfactant protein C (SpC) promoter (52). Wnt5a transgenic lungs show an opposite phenotype to that of Wnt5a knockout lungs. These include reduced branching, dilation of distal airway and early onset of
Wnt5a regulates lung maturation is just beginning to branch morphogenesis. Mechanisms through which lial-mesenchymal crosstalk, which is essential for lung amongst the latter signalling pathways control epithelium-vascular growth, as reflected in decreased number of airways, dilation of distal airways and thinner epithelial-vascular walls and precocious differentiation of AT1 cells. Therefore, it is reasonable to conclude that Wnt5a exhibits at least two distinct functions during lung development. First, Wnt5a regulates branching morphogenesis during the pseudoglandular stage. Secondly, Wnt5a promotes onset of the saccular stage (the early stage in lung maturation) and cell differentiation during lung maturation. The mechanism through which Wnt5a regulates branching morphogenesis involves regulation of SHH signalling which in turn regulates FGF10 signalling (52). Interactions amongst the latter signalling pathways control epithelial-mesenchymal crosstalk, which is essential for lung branching morphogenesis. Mechanisms through which Wnt5a regulates lung maturation is just beginning to be revealed (see below).

Results from examination of Wnt5a function in species other than mouse have validated the observations and conclusions reviewed above. In the developing chick lung, overexpression of Wnt5a through transduction using an avian specific retrovirus disrupted lung growth, as reflected in decreased number of airways, dilation of distal airways and thinner epithelial-vascular layers (53). Consistent with the observation in the mouse lung, Wnt5a overexpression in the chick lung resulted in decreased Sihh expression. Importantly, overexpression of Wnt5a inhibited canonical WNT signalling and the phenotype caused by Wnt5a overexpression was partially rescued by a dominant-negative Ror2, suggesting Wnt5a may achieve its function through ROR2-mediated signalling (53).

The role of Rors in lung development was examined even before characterization of Wnt5a knockout lungs (54, 55). Both Ror1 as well as Ror2 knockout mice died within 24 h after birth due to respiratory dysfunction. Histological analysis revealed that both mutant lungs were hypoplastic with thickened septal walls and smaller alveolar sacculles. In 2003, Oishi et al. (56) reported that there are extensive similarities between Wnt5a and Ror2 knockout lungs. Furthermore, the authors demonstrated that Ror2 mediates Wnt5a-induced non-canonical WNT signalling in vitro. Subsequent in vivo studies showed that expression of the canonical WNT reporter, Axin2loxP/loxP, was increased in Ror2 knockout lungs (57). This indicates that Ror2-mediated signalling negatively regulates canonical WNT signalling activity, one of the reported functions of non-canonical WNT signalling (44). Collectively, these studies suggest that Wnt5a through ROR receptors activates non-canonical WNT signalling to regulate lung development. Indeed, our recent studies demonstrate that compound mutations in Ror1 and Ror2 genes blocks specific aspects of the Wnt5a overexpression phenotype in SpC-Wnt5a;Ror1+/−;Ror2+/−/C0/C0 lungs (Fig. 3). Therefore, studies on Ror knockout lungs not only revealed the functions of Ror in lung development but also provided in vivo information...

**Fig. 2 Multiplicity of non-canonical WNT pathways and their identified functions in the lung.** Binding of WNT ligands to individual or different combination of their receptors including FZD, ROR1, ROR2 or RYK activates multiple β-catenin-independent pathways. Amongst these, the PCP pathway and Ca"²⁺ pathway are the most studied and have been found to regulate multiple functions in the lung. Details of each intracellular pathway are not shown as they have been illustrated by previous reviews (28, 35, 36, 37). BEC, bronchial epithelial cell; SMC, smooth muscle cell; ECM, extracellular matrix; AT2, type 2 AEC.
towards enhanced understanding of WNT5a-ROR non-canonical WNT signalling.

Beside RORS, several members of the FZD family have also been reported to mediate non-canonical WNT signalling (28, 30). In the lung, FZD2-mediated non-canonical WNT signalling plays an important role in controlling the balance between stem/progenitor expansion and epithelial differentiation (58). Bronchioalveolar stem cell (BASC) is a population of SCGB1A1+SPC+ epithelial cell located at the junctions of bronchiole and alveoli. Expression of Fzd2 is reduced in Gata6 knockout lungs in which BASCs expand and epithelial differentiation is inhibited. Re-expression of Fzd2 in Gata6 knockout (Gata6<sup>−/−</sup>;SPC/cre) lung explants partially rescued the lung epithelial defects. This was achieved by repressing canonical WNT signalling. In support of this observation, decreasing β-catenin expression also rescued the Gata6 knockout phenotype. Recently, FZD2-mediated non-canonical WNT signalling was reported to regulate epithelial cell shape which controls airway patterning during lung branching morphogenesis (59). Therefore, genetic studies that target either the ligand (Wnt5a) or the receptors (Rors and Fzd2) collectively support a mechanism whereby non-canonical WNT signalling promotes lung maturation. This important function of non-canonical WNT signalling is achieved possibly by promoting epithelial cell differentiation, capillary development, as well as AMF differentiation during lung maturation (see below).

**Cell-Type-Specific Functions of Non-Canonical WNT Signalling in the Lung**

Recently, non-canonical WNT signalling has been reported to regulate migration, proliferation, apoptosis and differentiation of multiple cell types in the lung. WNT5a was found to be the major WNT ligand that activates the non-canonical WNT pathway in the lung. However, it should be noted that different intracellular pathways are activated depending on the cellular context (Table I).

**Noncanonical WNT signalling in endothelial cells**

A number of studies have shown that WNT5a-induced non-canonical WNT signalling is important in...
Table I. Non-canonical WNT signalling components identified in specific lung cells and lung functions

<table>
<thead>
<tr>
<th>Lung cell type</th>
<th>Ligands</th>
<th>Receptors</th>
<th>Intracellular pathways</th>
<th>Effects on canonical WNT signalling</th>
<th>Cellular activity</th>
<th>Identified functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cells</td>
<td>WNT5a</td>
<td>ROR2</td>
<td>JNK and CaMKII pathways</td>
<td>Repressed</td>
<td>Blood vessel and capillary formation</td>
<td>Maturity</td>
<td>(50, 53, 60, 61)</td>
</tr>
<tr>
<td>AT2 cells</td>
<td>WNT5a</td>
<td>?</td>
<td>PKC pathway</td>
<td>Promotes p300/β-catenin Interaction Repressed</td>
<td>AT2 cell maintenance and differentiation</td>
<td>Maturity and homeostasis</td>
<td>(51, 62)</td>
</tr>
<tr>
<td>BASCs</td>
<td>?</td>
<td>FZD2</td>
<td>?</td>
<td></td>
<td>Stem Cell Maintenance and Differentiation</td>
<td>Maturity</td>
<td>(58)</td>
</tr>
<tr>
<td>Epithelial progenitors</td>
<td>WNT5a</td>
<td>RhoA</td>
<td>JNK and p38 pathways</td>
<td>Not affected</td>
<td>Cell shape Proliferation and inflammation</td>
<td>Airway branching</td>
<td>(59)</td>
</tr>
<tr>
<td>BECs and AECs</td>
<td>WNT5a (BECs), WNT5a (AECs)</td>
<td>FZD2</td>
<td>?</td>
<td></td>
<td>ECM production</td>
<td>Airway remodeling and inflammation AEC repair (COPD)</td>
<td>(63–66)</td>
</tr>
<tr>
<td>Airway SMCs</td>
<td>WNT5a</td>
<td>JNK and NFATc1 pathways</td>
<td>?</td>
<td></td>
<td></td>
<td>Asthma</td>
<td>(67)</td>
</tr>
<tr>
<td>Fibroblast cells</td>
<td>WNT5a</td>
<td>FZD8, RYK, FZDI</td>
<td>?</td>
<td>Repressed</td>
<td>Fibroblast cell proliferation, differentiation, apoptosis, and ECM production</td>
<td>Maturation and UIP</td>
<td>(5, 68, 69)</td>
</tr>
<tr>
<td>Pulmonary arteries</td>
<td>WNT11</td>
<td>?</td>
<td>PCP pathway</td>
<td>Activated</td>
<td>Vascular remodelling (IPAH)</td>
<td></td>
<td>(70–72)</td>
</tr>
</tbody>
</table>

"?" indicates components to be determined.
of the underlying mechanism comes from another recent study in which WNT5a signalling was found to activate PKC and increase phosphorylation of p300 (51). This led to increased p300/β-catenin interaction, which promoted AT2 to AT1 cell transdifferentiation, identifying a novel mechanism of WNT5a signalling.

Non-Canonical WNT signalling in airway SMCs

In mice, the ventral side of the trachea and the outer sides of mainstem bronchi are covered with cartilaginous rings which maintain the rigidity of the upper airways. The dorsal side of the trachea and the inner sides of mainstem bronchi are covered by SMCs in the subepithelial region, while the intralobular conducting airways are wrapped entirely in sheaths composed of SMCs. Airway SMC defects and malfunction are associated with respiratory disease such as asthma (79). Recent studies demonstrate that non-canonical WNT signalling is critical for SMC function (67). Kumawat et al. (67) reported that airway SMCs express high levels of Wnt5a. Wnt5a levels are significantly increased in the SMCs of asthma patients. Further analyses revealed that WNT5a regulates extracellular matrix (ECM) expression via JNK and Ca²⁺ dependent signalling pathways. Importantly, the latter signalling pathway mediates TGF-β-induced ECM expression (67). Both inhibition of Ca²⁺ and JNK signalling and inactivation of the WNT receptor FZD8 and RYK attenuate the effects of TGF-β on ECM expression. These data indicate that non-canonical WNT signalling functions downstream of TGF-β signalling in regulation of ECM expression. Furthermore, it has been well documented that intracellular Ca²⁺ and Rho kinase play critical roles in SMC activities (79, 80). It is likely that non-canonical WNT signalling regulates multiple functions of SMCs via Ca²⁺ and Rho kinase.

Non-canonical WNT signalling in lung fibroblasts

Fibroblasts are the major component of lung interstitium with distinct functions. Using a microarray strategy, Boucherat et al. (68) compared gene expression profiles of neonatal lung fibroblasts on postnatal days (PN) 2, 7 and 21. Expression of Wnt5a and Fzd1 increased from PN2 to PN7 in rat lungs, which is correlated with the stages before and during alveolar formation, respectively. Treatment of neonatal rats with dexamethasone (Dex), which disrupts alveolar formation, resulted in decreased Wnt5a and Fzd1. These observations suggest an important role for WNT5a signalling in alveolar formation. Consistent with the latter, our recent study demonstrated that expression of Wnt5a is robustly increased in AMF progenitors during saccular stage lung development (5). This is associated with a reduction of canonical WNT activity. On the other hand, forced activation of canonical WNT signalling by deletion of Apc gene expanded the AMF progenitor population in E18 mouse lungs. Therefore, downregulation of canonical WNT signalling by WNT5a-induced non-canonical WNT signalling in AMF progenitors may be a critical mechanism for precisely controlled differentiation of AMF, which are in turn necessary for alveolar formation.

Non-canonical WNT signalling also plays an important role in adult lung fibroblasts. Vuga et al. (69) compared gene expression profiles of lung fibroblasts from usual interstitial pneumonia (UIP) patients to that of normal lung fibroblasts. Expression of Wnt5a was significantly increased in UIP fibroblasts. Further analysis revealed that WNT5a promoted proliferation, increased fibronectin expression and inhibited H₂O₂-induced apoptosis in lung fibroblasts. These functions of WNT5a are associated with decreased β-catenin levels. Therefore, aberrant activation of WNT5a non-canonical WNT signalling may be instrumental in promoting UIP as well as other fibrotic lung diseases with UIP histology.

Non-Canonical WNT Signalling in Lung Diseases

As discussed above, non-canonical WNT signalling has been shown to be closely linked to lung diseases such as asthma and UIP (67, 68). In the lung of Mycobacterium tuberculosis infected patients, expression of WNT5a and FZD5 is significantly increased in the granulomatous lesions. Both WNT5a and FZD5 are required for antigen-triggered IFN-γ release and mycobacteria-induced IL-12 release by peripheral-blood mononuclear cells (81). Since WNT5a and FZD5 are known to activate the non-canonical WNT pathway (82, 83), it is likely that non-canonical WNT signalling mediates the latter functions of WNT5a and FZD5 in antimicrobial defence.

Chronic obstructive pulmonary disease (COPD) is a debilitating condition that involves inflammation and thickening of the airways and destruction of lung parenchymal tissue (emphysema). Durham et al. (63) found that Wnt4 is increased in bronchial biopsy samples from COPD patients. WNT4 acts through the non-canonical pathway to activate epithelial cell remodelling and IL-8 expression. Since cigarette smoking is closely associated with COPD, Heijink et al. (64) studied the effects of cigarette smoke extract (CSE) on BECs. They found that WNT4 increases CSE-induced pro-inflammatory cytokine release. These studies indicate that WNT4 induced non-canonical WNT signalling may stimulate airway inflammation in COPD. In emphysematous COPD patients, the regenerative capacity of AECs is impaired, possibly related to reduced canonical WNT activity. It has recently been shown that WNT5a non-canonical WNT signalling is increased in elastase- or cigarette smoke-induced COPD mouse models (65). The same authors further demonstrated that WNT5a attenuates canonical WNT signalling which is decreased in COPD tissues. Importantly, activation of canonical WNT signalling promotes repair of AECs from COPD patients (66).

Aberrant activation of non-canonical WNT was also observed in idiopathic pulmonary arterial hypertension (IPAH). Several mediators of the PCP pathway are strongly up-regulated in IPAH as compared with healthy lung tissues (70). Of note, canonical WNT
signalling is also activated in IPAH tissue. It has been reported that both canonical and non-canonical WNT signalling are involved in BMP2-induced angiogenesis (71). In pulmonary arterial endothelial cells both pathways are activated. WNT/PCP pathway induced motility while the canonical WNT pathway promoted cell proliferation. In comparison, in pulmonary arterial SMCs, the canonical WNT pathway and WNT/PCP pathway are sequentially activated to mediate BMP2-induced motility (72). Therefore, activity of both WNT pathways has to be properly controlled during angiogenesis and abnormal activation may lead to IPAH.

In lung cancer, especially non-small cell lung cancer (NSCLC), aberrant activation of both canonical as well as non-canonical WNT signalling promotes tumorigenesis (35, 84). These have been shown by multiple studies and are summarized in a recent review (29). In certain types of NSCLC such as squamous cell carcinoma, non-canonical WNT signalling has been found to down-regulate the canonical pathway. However, this is not associated with improved prognosis. Instead it leads to decreased cell–cell adhesion and increased epithelial-mesenchymal transition (85). Therefore, non-canonical WNT signalling seems to increase aggressiveness and invasiveness in most lung cancers (35, 84, 86). In summary, non-canonical WNT signalling may be a critical pathway that underlies the pathogenesis of several lung diseases and may serve as a key potential therapeutic target in devising and developing novel and effective treatments for these lung diseases.

Conclusions

The collective evidence reviewed above clearly shows that the non-canonical WNT pathway renders multiple key functions in lung development, homeostasis and diseases. These functions involve regulating various cellular activities through distinct intracellular pathways. At least as a part of its role in lung development and disease, the non-canonical WNT pathway provides a mechanism for regulating canonical WNT signalling and thus, the molecular and cellular functions that are under its control. In most cases, non-canonical WNT signalling represses canonical WNT activity. Interestingly, in AT2 cells, WNT5a-PKC signalling positively regulates specific aspects of canonical WNT activities, adding to the diversity of non-canonical WNT functions. Therefore, studies on non-canonical WNT signalling in the lung have not only revealed important mechanisms underlying various lung functions and diseases, but also enriched our understanding of WNT pathways in general.

Many of the conventional knockout mouse models that target the non-canonical WNT pathway result in perinatal lethality. Therefore, functions of the non-canonical WNT signalling in lung homeostasis and injury repair mechanisms have not been fully characterized. Much of the collected information has emerged from either in vitro studies or alteration of non-canonical WNT signalling in animal models that also carry other mutations. In recent years, a number of new tools have been developed that enable regulatable, conditional genetic manipulation of WNT pathway components under specific experimental settings (59, 87–94). Availability of these tools should pave the way to directly determine the role of the non-canonical WNT pathway in different aspects of lung biology and pathophysiology.

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Conflict of Interest

None declared.

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