# Role of the Wnt Signaling Pathway and Lung Cancer

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The Wnt pathway plays an important role in development and in regulating adult stem cell systems. A variety of cellular processes are mediated by Wnt signaling, including proliferation, differentiation, survival, apoptosis and cell motility.[1] Loss of regulation of these pathways can lead to tumorigenesis and the Wnt pathway has been implicated in the development of several types of cancers, including colon, lung, leukemia, breast, thyroid, and prostate.[2–6]

## WNT SIGNALING

Wnts are a family of secreted glycoproteins with varying expression patterns and a range of functions. Four signaling pathways are typically described for Wnt proteins. The canonical Wnt-$\beta$ catenin pathway, through which $\beta$-catenin dependent activity occurs, the polar cell polarity (PCP) pathway, involving activation of AP1 through JNK, an atypical receptor tyrosine kinase (RTK) pathway, and the Ca2+ pathway, which activates protein kinase C and affects cell adhesion.[7] In the unstimulated canonical pathway, $\beta$-catenin is phosphorylated by glycogen synthase kinase (GSK-3) in a complex that includes adenomatous polyposis coli (APC) and axin.[8] Phosphorylation targets $\beta$-catenin for ubiquitin-mediated degredation and results in decreased levels of cytosolic $\beta$-catenin (Table 1).

Binding by the Wnt ligant to the frizzled (Fzd) receptors are complexed with low density lipoprotein receptor related protein (LRP) resulting in inhibition of the GSK-3/APC/Axin complex by Disheveled (Dvl). $\beta$-catenin is not phosphorylated by the complex and accumulates in the cytoplasm where it is translocated to the nucleus and regulates gene expression through a complex with Tcf and Lef.[7] In the noncanonical pathways, signaling is conducted independent of $\beta$-catenin, though there may be similar components upstream of Fzd. The activity of different Wnt proteins is dependent on the receptor context, making strict classification of Wnts as canonical or noncanonical very challenging[9] (Figure 1).

Fzd receptors are involved in canonical and noncanonical Wnt signaling by binding Wnt at a CRD region and have been shown to specify downstream activity through G-proteins. Binding of the LRP receptor to Fzd, however, occurs only in the canonical pathway.[10] Other Wnt pathway receptors include atypical RTKs Ror and Ryk. Several ligands not structurally related to Wnt also influence the Wnt signaling pathway, including antagonists sFRP, DKK, SOST, and agonists Norrin and R-spondin.[11]

## WNT SIGNALING IN NORMAL LUNG DEVELOPMENT

Wnt signaling appears to regulate cell fate and differentiation in early embryogenesis through several components that are present in the developing lung.[12] Wnt production may be specific to cell type, such as Wnt 2 in the mesenchyme, Wnt 7b in the epithelium, and Wnt 11 in both locations.[8] Wnt 7b has been shown to be regulated by Thyroid Transcription Factor-1, which is important for differentiation of alveolar epithelial cells.[13] Other Wnt pathway components, such as Frizzled and Tcf, have been detected in specific patterns in the developing lung.[14] Wnt 7b null mice have hypoplastic lungs and impaired alveolar type I cell differentiation.[15] Wnt 5a is expressed in the lung epithelium and mesenchyme early development at the distal tips. Loss of Wnt 5a in mice results in increased proliferation in the epithelium and mesenchymal compartments, increased distal branching, and thickened interstitium.[16] Wnt 5a null mice have increased expression of Sonic Hedgehog, a tightly regulated protein involved in branching morphogenesis, suggesting that Wnt 5a interacts with other signaling pathways in lung development. However, a model using targeted deletion of $\beta$-catenin suggests that disruption of Wnt signaling leads to decreased branching morphogenesis.[17] Continued study is needed to clarify the role of Wnt signaling in branching morphogenesis. Wnt signaling may also play a role in apical-basal polarity and organogenesis, as changes in expression of polarity complex components have been found to affect Wnt signaling and the Wnt pathway itself may affect apical basal polarity.[18]

## WNT SIGNALING AND LUNG CANCER

Much of the research done on the Wnt pathway and cancer has been done in colon tumors, however, recent work highlights a potentially significant role for Wnt pathway components in lung cancer. Wnt 1 and Wnt 2 are overexpressed in NSCLC and their inhibition leads to apoptosis.[19]

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**TABLE 1.** Dysregulation of Wnt Pathway in Cancer

| Pathway Component | Type of Cancer |
|---|---|
| Increased Wnt-1 | Prostate,[32] Head and Neck,[33] Breast[34] |
| Increased Wnt-2 | Breast[35] |
| Decreased Wnt5a | Colorectal,[36] Neuroblastoma,[37] Thyroid,[38] Breast[39] |
| Increased Wnt7a | Colorectal,[40] Gastric,[40] Endometrial,[41] |
| Decreased Wnt7a | Lung[20,42] |
| Increased DVL | Breast,[4] Lung,[30] Mesothelioma[30] |
| Increased LRP5/LRP6 | Colorectal[43] |
| Increased Fzd2 | Gastric[44] |
| Increased Fzd3 | Leukemia[45] |
| Increased Fzd5 | Kidney[46] |
| Increased Fzd7 | Liver[47] |
| Increased Fzd8 | Gastric[44] |
| Increased Fzd9 | Astrocytoma,[48] Gastric[44] |
| Decreased sFRP | Liver,[49] Breast,[4] Bladder,[50] Head and Neck,[51] Leukemia,[52] Mesothelioma,[53] Colorectal[54] |
| Increased DVL | Breast,[4] Lung,[30] Mesothelioma[55] |
| Decreased APC | Gastrointestinal,[56] Breast,[57] Kidney[58] |
| Decreased Axin | Oral,[59] Liver,[60] Lung[61] |
| Increased β-catenin | Ovarian,[62] Hepatoblastoma,[63] Kidney[64] |

Fzd, Frizzled; DVL, Disheveled; LRP, sFRP, Secreted Frizzled-Related Protein; APC, Adenomatous Polyposis Coli.

Wnt 7a is of particular interest, as its re-expression has been reported to lead to growth inhibition of NSCLC cell lines through ERK5-dependent activation of Peroxisome Proliferator-Activated Receptor Gamma.[20,21] This pathway seems to be required for the maintenance of normal epithelial differentiation and represents noncanonical signaling by the Wnt pathway.

Disheveled proteins are overexpressed in NSCLC and are a route for Wnt/Fzd activation of Rac and Rho, which are known to be involved in lung carcinogenesis.[22] WIF-1, an antagonist of Wnt signaling, is silenced by promoter methylation in NSCLC and is able to inhibit cell growth in vitro and in vivo.[23] APC and sFRP1 are also methylated in lung adenocarcinoma, often concomitantly with WIF-1.[24] Evaluation of chromosomal aberrations and changes in gene expression in NSCLC found that WIF1, CTNNBIP1, and WISP2 (antagonists of the Wnt pathway) were underexpressed and LEF1 and Ruvbl1 (agonists) were overexpressed.[25] DKK1, an antagonist of Wnt signaling, is expressed in NSCLC cell lines, while sFRPs are downregulated.[22,26] These findings suggest roles for Wnt pathway components in tumorigenesis, though more work is needed to clarify the biological effects of pathway disruption.

## WNT SIGNALING PATHWAY AS A THERAPEUTIC TARGET

The Wnt pathway may play a significant role in lung tumor initiation and progression, thus providing opportunities for therapeutic intervention. Therapuetic interference with the Wnt pathway could be conducted at several levels. Restoration of SFRP4 function in cancer cells weakens Wnt signaling and induces apoptosis in NSCLC cell lines.[27] Interference with Wnt 1 signaling by siRNA or antibody induces apoptosis in cancer cells and inhibits tumor growth in vivo.[28] siRNA for

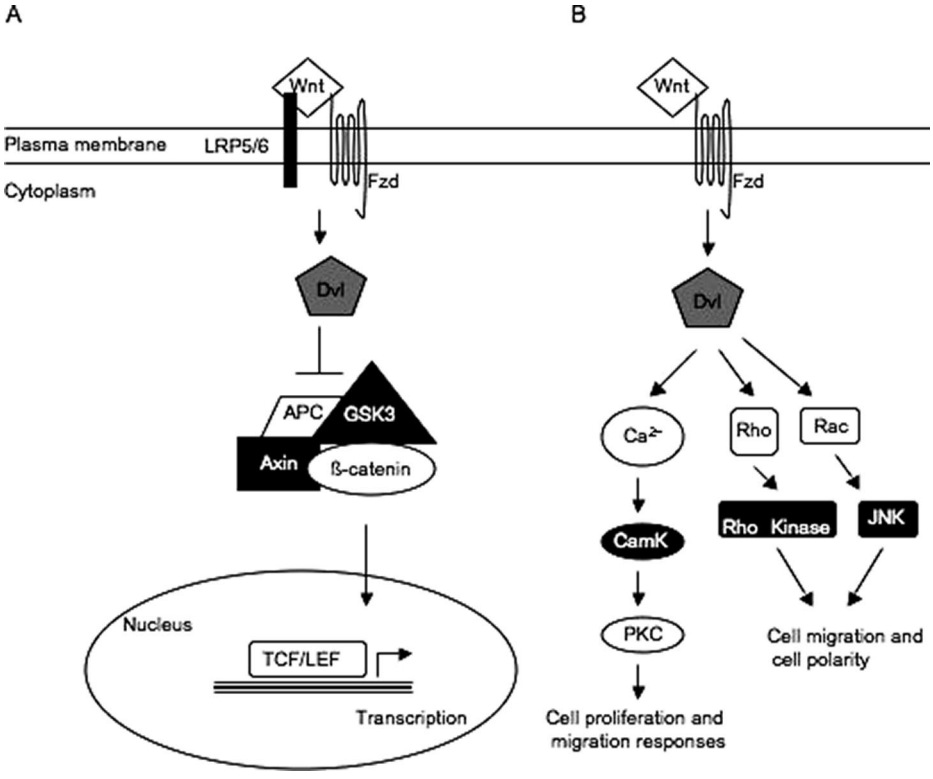


**FIGURE 1.** Wnt/β-catenin signaling. **(A).** Canonical pathway. **(B).** Noncanonical pathway. APC, adenomatous polyposis coli; Dvl, disheveled; GSK3, glycogen synthase kinase; Fzd, Frizzled; TCF, T-cell factor; LEF, lymphoid enhancer factor; JNK, c-jun N-terminal kinase; PCK, protein kinase C; CamK, calmodulin kinase II.

Wnt 2 downregulates β-catenin and induces apoptosis in NSCLC.[29] Restoration of Wnt 7a expression has been shown to reverse transformation in NSCLC and may be one approach to therapy through Wnt signaling.[20] Reduction of Disheveled overexpression by siRNA leads to a decrease in β-catenin expression and Tcf transcription activity in NSCLC.[30] A small molecule inhibitor, ICG-001, antagonizes β-catenin/Tcf transcription activation and downregulates β-catenin/Tcf responsive genes.[31]

The Wnt pathway, along with the Hedgehog pathway, is activated by smoke in bronchial epithelial cells and treatment with Sulindac, a Wnt pathway specific inhibitor, resulted in decreased tumor mass and volume in mice.[31] This may be an opportunity for inhibition of early stage tumorigenesis in the lungs of smokers. Proper apical/basal polarity has been implicated in cell cycle control and cell-cell adhesion, both processes disrupted in tumorigenesis, and as the role of Wnt signaling in this process is clarified, interventions in this pathway that lead to restoration of apical basal polarity may be therapeutic options.[18]

Investigations into the role of Wnt signaling in the lung have clearly begun to elucidate the importance of this pathway in lung cancer, however, there is still much to be done. The participation of different Wnt proteins in different pathways complicates the determination of the effects of changes in Wnt expression, as does the presence of many levels of regulation along the pathway. The diversity of Wnt signaling, however, provides a bounty of opportunity for development of desperately needed targeted therapy for lung cancer.

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