Introduction

WNT1-inducible signaling pathway protein 1 (WISP1), also known as CCN4, is a member of the cysteine-rich CCN family of growth factor proteins. Cysteine-rich angiogenic protein 61 (CYR61/CCN1), connective tissue growth factor (CTGF/CCN2), and nephroblastoma over expressed protein (NOV/CCN3) were the first discovered proteins in the family, so the acronym CCN stems from them; together with three WNT-induced secreted proteins, they comprise the CCN family of matricellular proteins [1,2].

The CCN protein family includes:
CCN1= CYR61 (cysteine-rich angiogenic protein 61) [3]
CCN2= CTGF (connective tissue growth factor) [4]
CCN3= NOV (nephroblastoma overexpressed) [5]
CCN4= WISP1 (WNT1-inducible signaling pathway protein-1) [2]
CCN5= WISP2 (WNT1-inducible signaling pathway protein-2) [6]
CCN6= WISP3 (WNT1-inducible signaling pathway protein-3) [7]

The CCN protein family secretes extracellular matrix (ECM)-associated proteins and is related to a variety of important cell function pathways, including mitosis, chemotaxis, adhesion, migration, survival, and differentiation, as well as cartilage formation, angiogenesis, tumor formation, and wound healing. CCNs have also been implicated in many human diseases [8-10]. WISP1/CCN4 is a member of the CCN protein family. Abnormalities of the WISP1 signaling pathway lead to a variety of pathological phenomena, such as fibrosis, osteoarthritis, and even cancer. Many respiratory diseases, such as pulmonary fibrosis, lung cancer, pulmonary inflammation, and ventilator-induced lung injury (VILI), are also associated with the WISP1 protein. The role of WISP1 in the occurrence and development of disease are reviewed [11,12]. Here, we focus on the impact and mechanism of WISP1 in pulmonary disease and summarize recent studies in which WISP1 has been shown to hold promise as a diagnostic marker and/or therapeutic target.

Structure

A classical CCN protein contains an N-terminal secretory signal peptide and four functional domains:

(i) An insulin-like growth factor binding protein-like module (IGFBP);
(ii) A von Willebrand factor type C repeat module (VWC);
(iii) A thrombospondin type-1 repeat module (TSP-1); and
(iv) A cysteine-knot-containing module (CT) (Figure 1) [2].

The CCN protein family includes:
CCN1= CYR61 (cysteine-rich angiogenic protein 61) [3]
CCN2= CTGF (connective tissue growth factor) [4]
CCN3= NOV (nephroblastoma overexpressed) [5]
CCN4= WISP1 (WNT1-inducible signaling pathway protein-1) [2]
CCN5= WISP2 (WNT1-inducible signaling pathway protein-2) [6]
CCN6= WISP3 (WNT1-inducible signaling pathway protein-3) [7]
A full length WISP1 consists of four modules: insulin-like growth factor binding domain (IGFBP) in red, von Willebrand factor C repeat (VWC) in blue, thrombospondin type-1 repeat (TSP-1) in yellow, and cysteine knot (CT) in green. The protein is split into two halves separated by a variable ‘hinge’ region. Different binding partners of each module are also depicted: insulin-like growth factors (IGFs); bone morphogenetic protein 4 (BMP4); transforming growth factor β (TGF-β); LDL receptor protein 1 (LRP-1); and heparin sulphated proteoglycans (HSPGs) (13).

Variation in CCN protein structure is related to the loss of one or more domains; the loss of different domains will result in different biological functions and ultimately lead to diseases (2). A full length WISP1 consists of four modules. Some studies have confirmed that invasive scirrhous gastric carcinoma (14) and cholangiocarcinoma (15) are related to the deletion of a module named VWC, reduced by alternative splicing of exon 3; WISP1 without the VWC module is referred to as WISP1v. Furthermore, besides full-length WISP1 and WISP1v, loss of more domains can be found in two hepatocellular carcinoma cell lines and a human chondrosarcoma-derived chondrocytic cell line, including ex 3-4 deltaWISP1 (16) and WISP1vx (17). Models of all described WISP1 variants are shown in (Figure 2) (18).

![Figure 2: Normal and abnormal molecular structures of CCN proteins: full length CCN4/WISP1 and truncated variants.](image)

The full length WISP1 protein consists of 367 amino acids with a predicted molecular mass of 40 kDa and has 38 conserved cysteine residues and four potential N-linked glycosylation sites (11,19). In fact, observations have shown that WISP1 is glycosylated, and the glycosylation patterns of WISP1 differ between types of cancer cells and healthy fibroblasts (20). In addition, due to the lack of mammalian post-translational modifications, over expressed WISP1 in mammalian cells and recombinant WISP1 produced in *Escherichia coli* produce different biological effects on cells (21). Based on these results, post-translational modifications seem to affect WISP1 function.

WISP1v is WISP1 deletion of a VWC module reduced by alternative splicing of exon 3 (14). WISP1vx lacks VWC and TSP1 domains and part of the IGFBP domain (23 bp shorter than the full-length exon). The IGFBP/CT fusion coding frame is not translated properly after the alternative splice site because of a frame-shift. The protein product is a single IGFBP module, in which eight C-terminal amino acid residues are removed, and an extra 14 residues are added in their place (17). WISP1Δex3-4 splice variant is a product of joining exons 2 and 5 with a frame shift that leads to a premature stop. As a result, the predicted protein has only the first module (16). SP: signal peptide, IGFBP: insulin growth factor binding protein, VWC: von Willebrand Factor protein has only the first module (16). SP: signal peptide, IGFBP: insulin growth factor binding protein, VWC: von Willebrand Factor C, TSP1: thrombospondin type 1 repeat, CT: C-terminal domain.

**Expression of WISP1 in disease**

WISP1 exists in many tissues and organs, such as epithelial tissue and the heart, kidney, lung, pancreas, placenta, ovary, small intestine, spleen, and brain (22), so it is related to the occurrence and development of many diseases. Cernea et al. (23) stated that WISP1 can be used as a new target gene for bone morphogenetic protein -3 (BMP3), and it was found that the BMP3/WISP1 signaling pathway plays an important role in the proliferation of mesenchymal stem cells and the process of lipid formation (23).

WISP1 has also been demonstrated as a possible target gene to treat esophageal squamous cell carcinoma. Zhang and his team found that WISP1 can enhance its own expression in response to radiation and form a positive feedback loop through which cancer cells increase their ability to resist radiation. So it can be considered a potential target for improving the sensitivity of esophageal cancer patients to radiotherapy (24).

Concurrently, the expression of WISP1 has been found to be higher in breast cancer cells than in normal breast tissue, and over expression of WISP1 inhibited the breast cancer tumor suppressor gene NDRG1 (25). WISP1 also plays a role in the growth and metabolism of bone. WISP1 is a negative regulator of osteoclast differentiation, which plays multiple roles in controlling bone homeostasis (26). Subsequently, WISP1 expression was found in osteoblasts and in the perichondrial mesenchyme by using a combination of *in situ* hybridization and immunohistochemistry (27). We may consider WISP1/CCN a prognostic marker in certain diseases such as pancreatic ductal adenocarcinoma and lymph nodemetastasis in oral squamous cell carcinoma (28,29).

WISP1 has also been found to play a role in many pulmonary diseases. Gavin BJ et al. (30) first reported WISP1 in the lungs in 1990 (30). WISP1 was then also found in various tissues and organs and was found to be expressed in various types of cells; thus, studies on WISP1 have attracted increasing attention (19). Diseases with increased morbidity and mortality such
Research on WISP1 in Lung Disease

Copyright: ©2016 Xia et al.

The most challenging therapeutic regimen issues could be solved if a biomarker could be found to represent a potential downstream mediator for therapeutic intervention in pulmonary fibrosis. Recently, studies on WISP1 in pulmonary fibrosis has increased. Stephan Klee et al. [31] reported that WISP1 expression was regulated by several profibrotic growth factors and that canonical signaling and ALK4/5/7 play critical roles in WISP1 expression induced by TGFβ[31]. Also, in the course of pulmonary fibrosis, the expression of WISP1 induced by TGF-β1 is regulated by miR-92a [32]. Different types of lung cells will produce different effects under recombinant WISP1 pretreatment. Pretreatment of type II airway epithelial cells (AECs) led to increased proliferation of type II AECs and epithelial-mesenchymal transition, whereas treating fibroblasts enhanced the deposition of the ECM [33,34]. Interestingly, neutralizing monoclonal antibodies specific for WISP1 attenuated bleomycin-induced lung fibrosis in mice [33].

Several WNT signaling proteins, including WNT1, WNT2, and WNT7A, are differentially expressed in lung cancer cells. WNT1 is related to lung cancer [35,36]. He et al. [36] reported that cancer cells expressing WNT1 are resistant to apoptotic therapies [36]. In contrast, anti-WNT1 monoclonal antibodies can suppress tumor growth in vivo [35]. As a WNT1 wingless pathway target gene, alterations of WISP1 have been reported in lung cancer specimens [20,37,38]. Usually, tumor progression has been associated with WISP1 expression; expression of WISP1 in lung cancer cells was significantly higher compared with healthy lung tissues. Chen et al. [37] and Yang et al. [39] found that the expression of WISP1 in lung adenocarcinoma was significantly higher than that in healthy lung tissues, but they did not find a correlation between WISP1 level and prognosis [37,39]. The gene polymorphism of WISP1 may also be used in the study of patients with lung cancer. Chen et al. [40] recruited 556 patients with lung cancer and 254 healthy controls and their results showed that several genotypes of WISP1 were associated with susceptibility to lung cancer and several WISP1 genotypes were significantly related to the efficacy of platinum-based chemotherapy in lung cancer patients. This finding can be used to predict the toxicity of platinum-based chemotherapy in lung cancer patients [41]. The emergence of various studies [39,40-42] on WISP1 may reveal it to be a novel and useful biomarker for the diagnosis and treatment of lung cancer.

Asthma is a chronic inflammatory disease. Previous research has focused on pre-survival and pro-fibrogenic signaling pathways, which are closely related to the remodeling of airway tissue. Along with further research, the WNT signaling pathway has been considered promising to further explore the molecular mechanism of organ fibrosis and tissue remodeling. Trischler et al. [43] reported that activation of the WNT signaling pathway, especially WISP1, is related to the airway remodeling process [43]. Both Sharma and Yang reported that WISP1 expression was correlated with asthma airway remodeling [44-46].

WISP1 is also involved in acute lung injury (ALI). The extensive use of anesthesia ventilators has contributed to an increase in VILI. The gene-encoding proteins of the CCN family, especially WISP1, are extremely sensitive to changes in the environment including mechanical stretch [2], however, the specific mechanism of the protein in various stretch-induced lung injury is not clear. Li and colleagues demonstrated that WISP1/CCN4, identified by a genome-wide approach, acts as a cellular accessory molecule that leads to VILI in mice [47]. Alveolar-capillary permeability, which can be used to determine the extent of lung injury, is actually proportional to WISP1-secreted in vivo after high tidal volume ventilation. Heise [48] found that WISP1 is significantly up-regulated in stretched type II epithelia in a hyaluronan- and MyD88-dependent fashion; meanwhile, the epithelial mesenchymal transition in stretched cells can be prevented by using WISP1 antibody. Faisyet al. [49] have also identified that stretch led to significantly higher mRNA levels of WISP1.

In addition to the correlation between WISP1 and pulmonary disease, the expression of WISP1 has been observed during lung development. Sharma et al. [45] confirmed that the WISP1 gene was associated with intrauterine airway development.

WISP1 and the WNT pathway

WISP1 has been suggested to act as a putative downstream effector of the WNT pathway [19]. The WNT signaling pathway is activated via two distinct branches: the canonical and non-canonical pathways, based on the expression profiles of receptors, co-receptors, and the activity of intracellular WNT signaling regulators [50,51]. The hallmark of the canonical WNT/β-catenin pathway is that it activates the transcription factor β-catenin, a downstream effector of the pathway that is initiated by WNT ligands to form a Frizzled receptor and low density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptor complex that inactivates glycogen synthase kinase-β (GSKβ) to block β-catenin phosphorylation and degradation that leads to accumulation of hypophosphorylated β-catenin in the cytoplasm and subsequent translocation to the nucleus, where it regulates target gene expression through interactions with a family of transcription factors [52-54].

Actually, the functional β-catenin/TCF heterodimeric transcription factor has been visualized in vivo, where β-galactosidase has been placed downstream from promoter elements harboring canonical TCF cis elements (e.g., TCF-optimized promoter-LacZ or TOPGal mice) [55]. These TOPGal mice have provided a sensitive approach for dissecting the role of the canonical β-catenin pathway in lung development [56], injury [57], and repair [58,54], as well as airway epithelial lineage and stem cell studies [59]. Pharmacological approaches to dissect the contribution of WNT/β-catenin canonical signaling include activation by lithium chloride, a well-known inhibitor of GSK-3β [58], or inhibition by using ICG-001, a selective inhibitor of WNT/β-catenin-dependent transcription [60]. Recently, the convergence of WNT/β-catenin canonical signaling, WISP1, and lung epithelial cell repair was demonstrated after inflammatory lung injury [61]. Extrapolation of the reparative role of WISP1 needs to put into context, as reviewed by Lawson and Blackwell [62]. Li [47] noted that WISP1 enhances alveolar capillary permeability in ALI and Konigshoff et al. [63] demonstrated that anti-WISP1 antibodies attenuated bleomycin-induced lung fibrosis. Fewer reagents and progress in the lung with respect to the non-
Research on WISP1 in Lung Disease

Xia YF, Chang J, Yang JF, Zhang LM (2016) Research on WISP1 in Lung Disease. J Anesth Crit Care Open Access 4(2): 00133. DOI: 10.15406/jaccoa.2016.04.00133

shown to play a critical role in ALI induced by high tidal volume [81], and transmitting biochemical signals through the MyD88 reaction by interacting with CD14 extracellular membrane in the TLR1-9 family that activates the cellular inflammatory immune response in sensing and responding to cellular injury in toluene inhalation [79]. TLRs play a pivotal role in the innate clinical depression, chronic fatigue syndrome, alcohol abuse, and inflammatory disorders, schizophrenia, bipolar disorder, autism, obesity, metabolic syndrome, autoimmune disorders, neuro-inflammatory disorders, schizophrenia, bipolar disorder, autism, clinical depression, chronic fatigue syndrome, alcohol abuse, and toluene inhalation [79]. TLRs play a pivotal role in the innate immune response in sensing and responding to cellular injury in the lung [80].

Activation of the TLR complex, a receptor of the innate immune system, may underpin the pathophysiology of many human diseases, including asthma, cardiovascular disorders, diabetes, obesity, metabolic syndrome, autoimmune disorders, neuro-inflammatory disorders, schizophrenia, bipolar disorder, autism, clinical depression, chronic fatigue syndrome, alcohol abuse, and toluene inhalation [79]. TLRs play a pivotal role in the innate immune response in sensing and responding to cellular injury in the lung [80].

TLR4 is the most important transmembrane protein receptor in the TLR1-9 family that activates the cellular inflammatory reaction by interacting with CD14 extracellular membrane [81], and transmitting biochemical signals through the MyD88 pathway [82] and TRIF intracellular pathway [83]. TLR4 has been shown to play a critical role in ALI induced by high tidal volume mechanical ventilation (HTV), [82,84,85], LPS[86], acid aspiration [87], hemorrhage [88], and ischemia and reperfusion injury [89]. Hu et al. [84] showed that HTV increases WISP1 expression [84]; meanwhile, mechanical stretch has been demonstrated to increase endogenous TLR4 ligand production and activate TLR4 in healthy mice [90,91]. Several studies have shown that TLR4 is associated with VILI in animal models [82,84, 90]. Zhang’s et al. [47] found that HTV can increase the expression and production of WISP1, which might contribute to VILI in mice; such a process probably occurs through modifying and/or enhancing TLR4-mediated cellular functions because the interaction between WISP1 with TLR4 is synergized. This includes both increased WISP1 production in HTV and activation of TLR4 signaling, leading to further lung injury.

WISP1 and toll-like receptor (TLRs), integrin-mediated signaling pathway

Mutual connections between WISP1 and TLRs and integrins are fairly complicated because of the wide variety of TLRs and integrins. The occurrence and development of many diseases are related to these connections. WISP1 (CCN4) is one of the CCN family proteins; the CCN proteins are key signaling and regulatory molecules involved in many vital biological functions, including cell proliferation, angiogenesis, tumorigenesis, and wound healing [67].

CCN proteins interact with cell surface integrins (e.g. cysteine-rich protein 61 (CCN1) via αvβ3 [68], CCN3 via αvβ5 [69], and WISP1 (CCN4) via αvβ3 [70] to induce intracellular signaling events [2,8]. Integrins appear to regulate inflammatory responses such as TNF release [71]. Indeed, RGD- (Arg-Gly-Asp-Ser peptides) sensitive integrin signaling in VILI [72] and αvβ3 and αvβ5 in particular have been identified to play critical roles in regulating pulmonary permeability in ALI and VILI [73].

Sheppard et al. [74,75] have demonstrated that β3 is protective (i.e.,β-null mice are sensitive) to endotracheal and intraperitoneal LPS and cecal ligation and puncture (CLP), whereas Pittet et al. have shown that β5 enhances (i.e.,β-null mice are resistant) to lung vascular leak after infection, [76] ischemia/reperfusion, or VILI [77]. Meanwhile, a new publication by Ding [78] suggested that the integrin family member β-6 is known to play an important role in regulating lung inflammation, macrophage protease expression, and pulmonary edema during the process of ALI. In this process, both WISP1 and integrin β6 constitute a pathway to regulate pathophysiologic process in the lung. Also, RGDs, which act as an inhibitor of integrin-ligand interactions, can block the pathway to alleviate ALI induced by CLP and improve the survival rate of mice.

Acknowledgement

This research was supported by NIGMS R01GM108639-01A1 grant 1151456 to Zhang. We thank Ms. Christine Heiner, Scientific Writer in the Department of Anesthesiology and Surgery at the University of Pittsburgh, for assistance with scientific editing that greatly improved the manuscript. We would also like to show our gratitude to Ms. Karla Woosloose, laboratory manager for providing comments on an earlier version of the manuscript.

References

1. Yeger H, Perbal B (2007) The CCN family of genes: a perspective on CCN biology and therapeutic potential. J Cell Commun Signal 1(3-4): 159-164.
2. Jun JI, Lau LF (2011) Taking aim at the extracellular matrix: CCN proteins as emerging therapeutic targets. Nat Rev Drug Discov 10(12): 945-963.
3. Lau LF (2011) CCN1/CYR61: the very model of a modern matricellular protein. Cell Mol Life Sci 68(19): 3149-3163.
4. Hall-Glenn F, Lyons KM (2011) Roles for CCN2 in normal physiological processes. Cell Mol Life Sci 68(19): 3209-3217.
5. Perbal B (2006) The CCN3 protein and cancer. Adv Exp Med Biol 587: 23-40.
Research on WISP1 in Lung Disease

6. Russo JW, Castellot Jr JJ (2010) CCN5: biology and pathophysiology. J Cell Commun Signal 4(3): 119-130.
7. Huang W, PaA, A, Klee CG (2012) On how CCN6 suppresses breast cancer growth and invasion. J Cell Commun Signal 6(1): 5-10.
8. Lai LF, Lam SCT (1999) The CCN family of angiogenic regulators: the integrin connection. Exp Cell Res 248(1): 44-57.
9. Brigstock DR (1999) The Connective Tissue Growth Factor/Cystine-Rich 61/Nephroblastoma Over expressed (CCN) Family I. Endocrin Rev 20(2): 189-206.
10. Perbal B (2001) The CCN family of genes: a brief history. Mol Pathol 54(2): 103-104.
11. Berschneider B, Königshoff M (2011) WNT1 inducible signaling pathway protein 1 (WISP1): a novel mediator linking development and disease. Int J Biochem Cell Biol 43(3): 306-309.
12. Gurbuz I, Chiquet-Ehrismann R (2015) CCN4/WISP1 (WNT1 inducible signaling pathway protein 1): A focus on its role in cancer. Int J Biochem Cell Biol 62: 142-146.
13. Holbourn KP, Acharya KR, Perbal B (2008) The CCN family of proteins: structure–function relationships. Trends Biochem Sci 33(10): 461-473.
14. Tanaka S, Sugimachi K, Saeki H, Kinoshiba J, Ogita T, et al. (2001) A novel variant of WISP1 lacking a Von Willebrand type C module overexpressed in scirrhous gastric carcinoma. Oncogene 20(39): 5525-5532.
15. Tanaka S, Sugimachi K, Kameyama T, Maeba A, Shirabe K, et al. (2003) Human WISP1IV, a member of the CCN family, is associated with invasive cholangiocarcinoma. Hepatology 37: 1122-1129.
16. Cervello M, GianniRapponi L, Labbozzetta M, Notarbartolo M, D'Allessandro N, et al. (2004) Expression of WISP4s and of their novel alternative variants in human hepatocellular carcinoma cells.Ann NY Acad Sci 1028: 432-439.
17. Yanagita T, Kubota S, Kawaki H, Kawata K, Kondo S, et al. (2007) Expression and physiological role of CCN4/Wnt-induced secreted protein 1 mRNA splicing variants in chordocytes. FEBS J 274(7): 1655-1665.
18. Gurbuz I, Chiquet-Ehrismann R (2015) CCN4/WISP1 (WNT1 inducible signaling pathway protein 1): A focus on its role in cancer. Int J Biochem Cell Biol 62: 142-146.
19. Pennica D, Swanson TA, Welsh JW, Roy MA, Lawrence DA, et al. (1998) WISP genes are members of the connective tissue growth factor family that are up-regulated in wnt-1-transformed cells and aberrantly expressed in human colon tumors. Proc Natl Acad Sci U S A 95(25): 14717-14722.
20. Soon LL, Ye TA, Shvarts A, Levine AJ, Su F, et al. (2003) Over expression of WISP1 down-regulated motility and invasion of lung cancer cells through inhibition Rac activation. J Biol Chem 278(13): 11465-1470.
21. Inkon CA, Ono M, Kuznetsov SA, Fisher LW, Robey PG, et al. (2008) TGF-beta1 and WISP-1/CCN-4 can regulate each other’s activity to cooperatively control osteoblast function. J Cell Biochem 104(5): 1865-1878.
22. Maiiese K, Chong ZZ, Shang YC, Wang S (2012) Targeting disease through novel pathways of apoptosis and autophagy. Expert Opin Ther Targets 16(12): 1203-1214.
23. Maria C, Wei T, Haiyan G, Yang K (2016) WISP1 mediates BMP3-stimulated mesenchymal stem cell proliferation. J Mol Endocrinol 56(1): 39-46.
24. Zhang H, Luo H, Hu Z, Peng J, Jiang Z, et al. (2015) Targeting WISP1 to sensitize esophageal squamous cell carcinoma to irradiation. Oncotarget 6(8): 6218-6234.
25. Chiang JC, Yeh CN, Chung LC, Feng TH, Sun CC, et al. (2015) WNT-1 inducible signaling pathway protein 1 enhances growth and tumorigenesis in human breast cancer. Sci Rep 5: 8866.
26. Maeda A, Ono M, Holmebeck K, Li L, Kilts TM, et al. (2015) WNT1-induced Secreted Protein-1 (WISP1), a Novel Regulator of Bone Turnover and Wnt Signaling. J Biol Chem 290(22): 14004-14018.
27. French DM, Kaul R J, D’Souza A L, Crowle OW, Bao M, et al. (2004) WISP1 is an osteoblastic regulator expressed during skeletal development and fracture repair. Am J Pathol 165(3): 855-867.
28. Yang JY, Yang MW, Huy YM, Liu W, Liu DJ, et al. (2015) High expression of WISP1 correlates with poor prognosis in pancreatic ductal adenocarcinoma. Am J Transl Res 7(9): 1621-1628.
29. Clausen MJ, Melters LJ, Mastik ME, Lorian SM, Harry JM, et al. (2016) Identification and validation of WISP1 as an epigenetic regulator of metastasis in oral squamous cell carcinoma. Genes Chromosomes Cancer 55(1): 45-59.
30. Gavin BJ, McMahon JA, McMahon AP (1990) Expression of multiple novel Wnt-1/Int-1-related genes during fetal and adult mouse development. Genes Dev 4(12B): 2319-2332.
31. Stephan K, Verena A, Barbara B, Melanie K (2014) Regulation of WISP1 by profibrotic cytokines in pulmonary fibrosis. European Respiratory Journal 44(Suppl58): 1417.
32. Berschneider B, Elwanger D C, Baarsma H A, Thiel C, Shimbori C, et al. (2014) miR-92a regulates TGF-β1-induced WISP1 expression in pulmonary fibrosis. Int J Biochem Cell Biol 53: 432-441.
33. Königshoff M, Kramer M, Balsara N, Wilhelm J, Amarie OV, et al. (2009) WNT1-inducible signaling protein–1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. J Clin Invest 119(4): 772-787.
34. Misemer BS, Skubitz APN, Carlos Manivel J, Schmechel SC, Cheng EY, et al. (2014) Expression of FAP, ADAM12, WISP1, and SOX11 is heterogeneous in aggressive fibromatosis and spatially relates to the histologic features of tumor activity. Cancer Med 3(1): 81-90.
35. Chen S, Guttridge DC, Yu Z, Zhang Z, Fribley A, et al. (2001) WNT-1 signaling inhibits apoptosis by activating beta-catenin/T cell factor-mediated transcription. J Cell Biol 152(1): 87-96.
36. He B, You L, Uematsu K, Xu Z, Lee AX, et al. (2004) A monoclonal antibody against WNTF1 induces apoptosis in human cancer cells. Neoplasia 6(1): 7-14.
37. Chen PP, Li WJ, Wang Y, Zhao S, Li DY, et al. (2007) Expression of Cyr61, CTGF, and WISP1 correlates with clinical features of lung cancer. PLoS One 2(6): e534.
38. Margalit O, Eisenbach L, Amarglio N, Kaminski N, Harelman A, et al. (2003) Over expression of a set of genes, including WISP-1, common to pulmonary metastases of both mouse D122 Lewis lung carcinoma and B16-F10.9 melanoma cell lines. Br J Cancer 89(2): 314-319.
39. Yang ZH, Zheng R, Gao Y, Zhang Q, Zhang H (2014) Abnormal gene expression and gene fusion in lung adenocarcinoma with high-throughput RNA sequencing. Cancer Gene Ther 21(2): 74-82.
40. Chen J, Yin J, Li X, Wang Y, Zheng Y, et al. (2015) Association of Wnt-Inducible Signaling Pathway Protein 1 Genetic Polymorphisms with Lung Cancer Susceptibility and Platinum-Based Chemotherapy Response. Clin Lung Cancer 16(4): 298-304.
41. Chen J, Yin J, Li X, Wang Y, Zheng Y, et al. (2014) WISP1 Polymorphisms
Contribute to Platinum-Based Chemotherapy Toxicity in Lung Cancer Patients. Int J Mol Sci 15(11): 21011-21027.

42. Xu Y, Lu S (2015) Role of WNT1-inducible-signaling pathway protein 1 in etoposide resistance in lung adenocarcinoma A549 cells. Int J Clin Exp Med 8(9): 14962-14968.

43. Goldklang M P, Sklepiewczik P, Shiomi T (1856) Activation of Wnt Signaling In Ashtmatic Airway Remodeling. Am J Respir Crit Care Med 187: 2013.

44. Yang M, Zhao X, Liu Y, Tian Y, Ran X, et al. (2013) A role for WNT1-inducible-signaling protein-1 in airway remodeling in a rat asthma model. Int Immunopharmacol 17(2): 350-357.

45. Sharma S, Tantisira K, Carey V, Murphy A, Lasky-Su J, et al. (2010) A role for Wnt signaling genes in the pathogenesis of impaired lung function in asthma. Am J Respir Crit Care Med 181(4): 329-336.

46. Yang M, Du Y, Xu Z, Jiang Y (2015) Functional Effects of WNT1-Inducible Signaling Pathway Protein-1 on Bronchial Smooth Muscle Cell Migration and Proliferation In OVA-Induced Airway Remodeling. Inflammation 1-14.

47. Li H, Li Q, Liu P, Li J, Wasserloos K, et al. (2012) WNT1-inducible signaling pathway protein 1 contributes to ventilator-induced lung injury. Am J Respir Cell Mol Biol 47(4): 528-535.

48. Heise R L, Stober V, Cheluvaraju C, Hollingsworth JW, Garantziotis S (2011) Mechanical stretch induces epithelial-mesenchymal transition in abeolar epithelia via hyaluronan activation of innate immunity. J Biol Chem 286(20): 17435-17444.

49. Faissy C, Pinto FM, Le Guen M, Naïne E, Grassin D, et al. (2011) Airway response to acute mechanical stress in a human bronchial model of stretch. Crit Care 15(5): R208.

50. Katoh M, Katoh M (2007) WNT signaling pathway and stem cell signaling network. Clin Cancer Res 13(14): 4042-4045.

51. Zerlin M, Julius M A, Kitajewski J (2008) Wnt/β-catenin signaling in angiogenesis. Angiogenesis 11(1): 63-69.

52. MacDonald BT, Tamai K, He X (2009) Wnt/β-catenin signaling: components, mechanisms, and diseases. Developmental cell 17(1): 9-26.

53. Moon RT, Kohn AD, De Ferrari GV, Kaykas A (2004) WNT and β-catenin signaling diseases and therapies. Nat Rev Genet 5(9): 691-701.

54. Zeng X, Huang H, Tamai K, Zhang X, Harada Y, et al. (2008) Initiation of Wnt signaling control of Wntcoreceptor Lrp6 phosphorylation/activation via frizzled, dishevelled and axinifications. Development 135(2): 367-375.

55. Zenke A C, Teisani R M, Giangreco A, Drake JA, Brockway BL, et al. (2009) β-catenin is not necessary for maintenance or repair of the bronchial epithelium. Am J Respir Cell Mol Biol 41(5): 535-543.

56. Al Alam D, Green M, Tabatabailrani R, Parta S, Danopoulos S, et al. (2011) Contrasting expression of canonical Wnt signaling reporter TOPGAL, BATGAL and Axin2 (LacZ) during murine lung development and repair. PLoS One 6(8): e23139.

57. Zemans RL, Briones N, Campbell M, McClendon J, Young SK, et al. (2011) Neutrophil transmigration triggers repair of the lung epithelium via β-catenin signaling. Proc Natl Acad Sci U S A 108(38): 15990-15995.

58. Kneklinger N, YildirimâM, Callegari J, Takanaka S, Stein MM, et al. (2011) Activation of the WNT/β-catenin pathway attenuates experimental emphysema. Am J Respir Crit Care Med 183(6): 723-733.

59. Smith RW, Hicks DA, Reynolds SD (2012) Roles for β-catenin and doxycycline in the regulation of respiratory epithelial cell frequency and function. Am J Respir Cell Mol Biol 46(1): 115-124.

60. Henderson WR, Chi EY, Ye X, Nguyen C, Tien YT, et al. (2010) Inhibition of Wnt/β-catenin/CREB binding protein (CRBP) signaling reverses pulmonary fibrosis. Proc Natl Acad Sci U S A 107(32): 14309-14314.

61. Zamans R L, McClendon J, Aschner Y, Briones N, Young SK, et al. (2013) Role of β-catenin-regulated CCN matrixcellular proteins in epithelial repair after inflammatory lung injury. Am J Physiol Lung Cell Mol Physiol 304(6): L4145-L427.

62. Lawson WE, Blackwell TS (2013) β-Catenin and CCNs in lung epithelial repair. Am J Physiol Lung Cell Mol Physiol 304(9): L579-L581.

63. Königinhoff M, Kramer M, Balsara N, Wilhelm J, Amarie OV, et al. (2009) WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. J Clin Invest 119(7): 772-787.

64. Bartis D, Csongel V, Weich A, Kiss E, Barko S, et al. (2013) Down-regulation of canonical and up-regulation of non-canonical Wntsignaling in the carcinogenic process of squamous cell lung carcinoma. PLoS one 8(3): e57393.

65. Bartis D, Csongel V, Weich A, Kiss E, Barko S, et al. (2013) Down-regulation of canonical and up-regulation of non-canonical Wntsignaling in the carcinogenic process of squamous cell lung carcinoma. PLoS one 8(3): e57393.

66. Villar J, Cabrera N E, Valladares F, Casula M, Flores C, et al. (2011) Activation of the Wnt/β-catenin signaling pathway by mechanical ventilation is associated with ventilator-induced pulmonary fibrosis in healthy lungs. PLoS One 6(9): e23914.

67. Blom AB, Brockbank SM, van Lent PL, van Beuningen HM, Geurts J, et al. (2009) Involvement of the Wnt signaling pathway in experimental and human osteoarthritis: Prominent role of Wnt-induced signaling protein 1. Arthritis Rheum 60(2): 501-512.

68. Qin Z, Fisher G J, Quan T (2013) Cysteine-rich protein 61 (CCN1) domain-specific stimulation of matrix metalloproteinase-1 expression through αvβ3 integrin in human skin fibroblasts. J Biol Chem 288(17): 12386-12394.

69. Lin G, Chen CC, Leu SJ, Grzeszkiewicz TM, Lau LF (2005) Integrin-independent Functions of the Angiogenic Inducer NOV (CCN3) implication in wound healing. J Biol Chem 280(9): 8229-8237.

70. Wu CL, Tsai HC, ChenZW, Wu CM, Li TM, et al. (2013) Ras activation mediates WISP-1-induced increases in cell motility and matrix metalloproteinase expression in human osteoarthritis. Cell Signal 25(12): 2812-2822.

71. Chen CC, Young JL, Monzon R, Chen N, Todorovic V, et al. (2007) Cytotoxicity of TNFs is regulated by integrin-mediated matrix signaling. EMBO J 26(5): 1257-1267.

72. Chen CC, Young JL, Monzon R, Chen N, Todorovic V, et al. (2007) Cytotoxicity of TNFs is regulated by integrin-mediated matrix signaling. EMBO J 26(5): 1257-1267.

73. Sheppard D (2012) Modulation of acute lung injury by integrins. Proc Am Thorac Soc 9(3): 126-129.

74. Bhattacharya M, Su G, Su X, Oses-Prieto JA, Li JT, et al. (2012) IQGAP1 is necessary for pulmonary vascular barrier protection in murine acute lung injury and pneumonia. Am J Physiol Lung Cell Mol Physiol 303(1): L12-L19.

75. Su G, Atakilat A, Li JT, Wu N, Bhattacharya M, et al. (2012) Absence of integrin αvβ3 enhances vascular leak in mice by inhibiting endothelial cortical actin formation. Am J Respir Crit Care Med 185(1): 58-66.
76. Ganter MT, Roux J, Su G, Lynch SV, Deutschman CS, et al. (2009) Role of small GTPases and αvβ5 integrin in Pseudomonas aeruginosa-induced increase in lung endothelial permeability. Am J Respir Cell Mol Biol 40(1): 108-118.

77. Su G, Hodnett M, Wu N, Atakilt A, Kosinski C, et al. (2007) Integrin αvβ5 regulates lung vascular permeability and pulmonary endothelial barrier function. Am J Respir Cell Mol Biol 36(3): 377-386.

78. Ding X, Wang X, Zhao X, Jin S, Tong Y, et al. (2015) RGD Peptides Protects Against Acute Lung Injury in Septic Mice Through Wisp1-Integrin β6 Pathway Inhibition. Shock 43(4): 352-360.

79. Lucas K, Maes M (2013) Role of the Toll Like receptor (TLR) radical cycle in chronic inflammation: possible treatments targeting the TLR4 pathway. Mol Neurobiol 48(1): 190-204.

80. Opitz B, van Laak V, Eitel J, Suttorp N (2010) Innate immune recognition in infectious and noninfectious diseases of the lung. Am J Respir Crit Care Med 181(12): 1294-1309.

81. Akashi S, Ogata H, Kirikae F, Kirikae T, Kawasaki K, et al. (2000) Regulatory roles for CD14 and phosphatidylinositol in the signaling via toll-like receptor 4-MD-2. Biochem Biophys Res Commun 268(1): 172-177.

82. Li H, Su X, Yen X, Wasserloos K, Chao W, et al. (2010) Toll-like receptor 4-myeloid differentiation factor 88 signaling contributes to ventilator-induced lung injury in mice. Anesthesiology 113(3): 619-629.

83. Gurung P, Malireddy RKS, Anand PK, Demon D, Vande Walle L, et al. (2012) Toll or interleukin-1 receptor (TIR) domain-containing adapter inducing interferon-β (TRIF)-mediated caspase-11 protease production integrates Toll-like receptor 4 (TLR4) protein-and Nlrp3 inflammasome-mediated host defense against enteropathogens. J Biol Chem 287(41): 34474-34483.

84. Hu G, Malik AB, Minshall RD (2010) Toll-like receptor-4 mediates neutrophil sequestration and lung injury induced by endotoxin and hyperinflation. Crit Care Med 38(1): 194-201.

85. Vaneker M, Heunks LM, Joosten LA, van Hees HW, Snijderlaar DG, et al. (2009) Mechanical Ventilation Induces a Toll/Interleukin-1 Receptor Domain-containing Adapter-inducing Interferon–Dependent Inflammatory Response in Healthy Mice. Anesthesiology 111(4):836-843.

86. Tanimura N, Saitoh S, Matsumoto F, Akashi-Takamura S, Miyake K (2008) Roles for LPS-dependent interaction and relocation of TLR4 and TRAM in TRIF-signaling. Biochem Biophys Res Commun 368(1): 94-99.

87. Imai Y, Kuba K, Neely GG, Yaghoubian-Malhami R, Perkmann T, et al. (2008) Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell 133(2): 235-249.

88. Lv T, Shen X, Shi Y (2009) TLR4 is essential in acute lung injury induced by unresuscitated hemorrhagic shock. J Trauma 66(1): 124-131.

89. Vaneker M, Joosten LA, Heunks LM, Snijderlaar DG, Halbertsma FJ, et al. (2008) Low-tidal-volume mechanical ventilation induces a Toll-like receptor 4-dependent inflammatory response in healthy mice. Anesthesiology 109(3): 465-472.

90. Gharib SA, Liles WC, Klaff LS, Altemeier WA (2009) Noninjurious mechanical ventilation activates a proinflammatory transcriptional program in the lung. Physiol Genomics 37(3): 239-248.

91. Maiese K (2014) WISP1: Clinical insights for a proliferative and restorative member of the CCN family. Curr Neurovasc Res 11(4): 378-389.