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WNT-INDUCIBLE PROTEIN (WISP-1) IS A KEY REGULATOR OF ALVEOLAR EPITHELIAL CELL HYPERPLASIA IN PULMONARY FIBROSIS

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WINNING ABSTRACT: Fibrotic lung disease is characterized by distorted lung architecture and severe loss of respiratory function secondary to alveolar epithelial cell (AEC) hyperplasia, enhanced extracellular matrix (ECM) deposition and fibroblast proliferation. Repetitive epithelial injuries with impaired alveolar wound healing and altered AEC gene expression represent a trigger mechanism for development of fibrosis. To reveal gene regulatory networks in lung fibrosis, we compared gene expression profiles of freshly isolated AEC obtained from mice 14 days after saline or bleomycin (BM) instillation using whole genome microarray analysis. Several genes of the Wnt signaling pathway, in particular WISP-1, a member of the CCN family, were highly regulated. WISP-1 protein expression was demonstrated in proliferating AEC in BM-treated lungs by immunofluorescence. When analyzing all six CCN family members, WISP-1 was upregulated the most 14 days after BM challenge, as analyzed by qRT-PCR. To elucidate WISP-1 function, cultured primary mouse AEC were stimulated with WISP-1 and demonstrated a 230% increase in proliferation, analyzed by 3H-thymidine incorporation. This was mediated through enhanced phosphorylation, but not expression of protein kinase B (PKB/Akt), as detected by immunoblot. Finally, increased expression of WISP-1 was detected in lung homogenates and isolated AEC from IPF patients, using qRT-PCR. Immunohistochemical analysis of WISP-1 and Ki67 verified the existence of hyperplastic and proliferative AEC expressing WISP-1 *in vivo*. Our study thus identifies WISP-1 as a novel regulator of AEC injury and repair, and suggests that WISP-1 is a key mediator in pulmonary fibrosis.

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MY JOB AND THE UNIT IN WHICH I WORK

I am currently pursuing my MD/PhD degree at the University of Giessen Lung Center (UGLC), Giessen, Germany, a collaborative and interdepartmental research initiative at the University of Giessen School of Medicine, focusing on translational lung research. The UGLC comprises 12 institutes and centres dedicated to basic and clinical research in a broad range of lung diseases. At this point in time, the UGLC represents a scientific network incorporating 20 research groups with >120 basic scientists and clinicians and a vast experience in respiratory medicine and molecular biology. Furthermore, integrated graduate programmes at the UGLC underscore its strong interest in scientific education in the pulmonary sciences. Among these graduate programmes, the International Graduate Program ''Molecular Biology and Medicine of the Lung (MBML)'' represents one of the few intercontinental training programmes in lung biology and pathology. My PhD project is integrated into the MBML graduate programme and is entitled ''Epithelial–mesenchymal interaction in lung fibrosis''. Here, my main scientific interest focuses on the function and interaction of two distinct cell types, alveolar epithelial cells and interstitial fibroblasts, and their role in the pathogenesis of lung fibrosis.

MY WINNING ABSTRACT AS PART OF MY RESEARCH

My PhD work, ''Epithelial–mesenchymal interaction in lung fibrosis'', analyses the role of alveolar epithelial cells and their contribution to the development of idiopathic pulmonary fibrosis (IPF). IPF represents a progressive and lethal disorder of major concern due to its unresolved pathogenesis and limited responsiveness to currently available therapies. Pathological features that are routinely observed in IPF include alveolar epithelial cell damage, increased deposition of extracellular matrix (ECM) in the lung interstitium, enhanced fibroblast/myofibroblast proliferation and activation, and, ultimately, distortion of normal lung architecture. The hallmark lesions of IPF are fibroblast foci, which are sites featuring activated myofibroblasts, synthesising and depositing a collagen-rich ECM. The number of α-smooth muscle actin-positive, activated (myo)fibroblasts is significantly increased in multiple forms of pulmonary fibrosis including IPF, but their origin remains to be elucidated. Currently, three major theories

attempt to explain the accumulation of activated (myo)fibroblasts in the lungs of IPF patients: 1) activation and proliferation of local (myo)fibroblasts; 2) infiltration and differentiation of circulating progenitor cells; and 3) a phenotypic transformation of alveolar epithelial cells to mesenchymal cells termed epithelial-to-mesenchymal transition (EMT). In all of these processes, alveolar epithelial cells and/or mediators secreted by these cells represent a key factor. The aim of my studies is to identify and characterise previously unknown mediators of alveolar epithelial cell signalling and fibrogenesis. To this end, we used an unbiased microarray approach identifying changes in the gene expression profile of primary mouse alveolar epithelial cells, freshly isolated from control or fibrotic mice. This experiment was the basis of the work presented in the winning abstract. We found Wnt-inducible signalling protein (WISP)-1, a downstream target in the Wnt pathway, to be involved in the regulation of proliferation and hyperplasia of alveolar epithelial cells. Currently, we are investigating the function of and therapeutic options for WISP-1 in lung fibrosis, which are the subject of my abstract.

MY RESEARCH AS PART OF MY WORKING GROUP/ RESEARCH TEAM

A defining role within the scientific network on the UGLC is exerted by the Collaborative Research Center (Sonderforschungsbereich) 547 ''Cardiopulmonary Vasculature'' funded by the Deutsche Forschungsgemeinschaft (DFG), the central public funding organisation in Germany. Closely affiliated are two clinical research groups (Klinische Forschergruppen) investigating projects related to ''Respiratory insufficiency'' and ''Pathomechanisms and therapy of lung fibrosis''. In addition, two junior research groups are specifically investigating the mechanisms of pulmonary fibrosis. I am currently part of the clinical research group ''Pathomechanisms and therapy of lung fibrosis'', which is structured into six projects. Within this research conglomerate, a broad spectrum of topics is covered: genetic predispositions to IPF, alterations of alveolar development, cell–cell/cell–matrix interaction, signal transduction of growth factors, coagulation and processing/ regulation of surfactant function. These projects also include clinical trials (*e.g.* Heparin Aerosol Application in Lung Fibrosis (HEALFIB)) that are closely connected with our outpatient department for lung fibrosis (http://www.uniklinikum-giessen.de/lufi/).

THE IMPACT OF MY WORK ON CLINICAL OR RESEARCH PRACTICE

The aim of our studies is to gain detailed insights into the pathomechanisms of lung fibrosis, a process that to date remains unclear. Our research is supported by the observation that alveolar epithelial cell injury and repair is an important trigger event in the development of lung fibrosis. It is unclear, however, whether increased apoptosis and/or proliferation represent a dominant pathogenetic mechanism in this disease. Using primary alveolar epithelial cells from a mouse model of experimental lung fibrosis, we have characterised the morphology and function of these cells. Our unbiased microarray approach uncovered, in addition to already-known mediators, WISP-1 as a novel secreted molecule that could play a key role in the process of lung fibrosis. The identification and characterisation of novel profibrotic mediators will have an impact as possible therapeutic targets and may help to influence progression of this severe disease. Since no effective therapeutic options for patients with IPF exist at this moment, future work in our group and others will unravel the regulation of WISP-1 as a profibrotic cytokine and whether this will open up new therapeutic options for patients with IPF.