



Research: Protective Role of Proteoglycans in Pulmonary Fibrosis

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Disease/Condition: Human and Experimental Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis (IPF) is a chronic progressive interstitial lung disease (ILD) that is largely unresponsive to medical treatment and is associated with a mean survival of 50% at 3-5 years. Despite extensive investigation, the cause of IPF remains unknown. The condition involves abnormal and excessive deposition of collagen (fibrosis) in the pulmonary interstitium (mainly the walls of the alveoli) with minimal associated inflammation. However, a consistent finding in animal models and lung samples obtained from IPF patients is the presence of injury and cell death of the cells that line the airway (alveolar epithelial cells). Increased alveolar epithelial cell (AEC) death may result in ineffective repair of the alveolar epithelium, thus promoting abnormal tissue repair.

Dr. Shi recently profiled alveolar macrophages obtained from IPF patients using a novel technology called micro-arrays, which allows investigators to interrogate the expression of thousands of genes in a single experiment. Syndecan-2, a membrane protein with a high content of glucose chains (proteoglycan), was one of highest expressed genes in the macrophages of IPF patients. In order to determine the role of proteoglycans, Dr. Shi, in collaboration with Brigham and Women's Hospital investigators, have generated a genetically modified mouse that expresses high levels of human syndecan-2, and a second mouse in which the syndecan-2 gene is deleted. Recent experiments show that mice that express high levels of human syndecan-2 are protected from bleomycin-induced pulmonary fibrosis. Using conventional molecular biology experiments, Dr. Shi and LRRRI scientists have determined a mechanism by which syndecan-2 can decrease the lung levels of TGF-beta, a protein that is known to induce pulmonary fibrosis in humans.

The results of this research suggest that alveolar macrophage syndecan-2 protects lung airway cells. Furthermore, these data suggest that alveolar macrophages have a role in promoting the resolution of pulmonary fibrosis. Ongoing studies will allow researchers at LRRRI to demonstrate the potential therapeutic role of proteoglycans in human pulmonary fibrosis.