

LTRC Concept Sheet # 07-99-0007

Regulation of Fibroblast Phenotype in Lung Fibrosis

ABSTRACT

Both the prevalence and the age-adjusted mortality of idiopathic pulmonary fibrosis (IPF) have increased in the past two decades. Despite extensive investigation into the pathophysiology of IPF, there is still no effective treatment for this fatal disease. Our lab has found that the absence of expression of Thy-1, a cell-surface glycoprotein, correlates with a profibrotic myofibroblast phenotype in lung fibrosis. We have evidence to suggest two possible mechanisms of Thy-1 regulation in lung fibrosis: ectodomain shedding and epigenetic regulation. These are both potentially reversible mechanisms to alter the profibrotic phenotype of lung fibroblasts.

Epigenetic/transcriptional regulation (e.g., promoter methylation, chromatin modification, miRNA) is a broad mechanism for durable/heritable (but potentially reversible) modification of cell phenotype in development, cancer, aging and in response to environmental stimuli. There is growing evidence that epigenetic regulation may be important in fibrotic disease (e.g., cirrhosis, scleroderma) as well. Our lab has found that Thy-1, an important “fibrosis suppressor” in the lung, is regulated by promoter hypermethylation and histone deacetylation in Thy-1(-) rat and human lung fibroblasts. Furthermore, we have preliminary evidence of hypermethylation of the *thy-1* promoter within fibroblastic foci (FF) of IPF by MSP-ISH. Inhibitors of DNA methyltransferase and histone deacetylase can restore Thy-1 expression and inhibit myofibroblastic differentiation in vitro. The latter finding is consistent with other recent in vitro studies in human skin fibroblasts. Taken together, these observations suggest that epigenetic/transcriptional regulation of *thy-1* and other fibrosis modulating genes may be a novel target in IPF or other pulmonary fibrotic conditions.

Additional evidence from our laboratory indicates that soluble Thy-1 is present in BALF from IPF patients, directly correlated with numbers of FF/mm², suggesting that Thy-1 may be a biomarker for fibrogenesis in IPF. Furthermore, identifying and inhibiting the mechanism of shedding may provide a novel therapeutic target.

We hypothesize that epigenetic regulation of the fibrosis suppressor Thy-1 occurs within fibroblastic foci of IPF and is correlated with myofibroblastic differentiation. Additionally, we hypothesize that proteolytic ectodomain shedding of Thy-1 from fibroblasts/fibrocytes further promotes fibrogenesis in the setting of acute inflammation.

Lung tissues (whole tissues and microdissected FF) from patients with mild (FEV₁ > 80%) and severe (FEV₁ <50%) chronic obstructive pulmonary disease (COPD) and IPF collected by the Lung Tissue Research Consortium will be analyzed for evidence of epigenetic regulation of Thy-1, as well as other genes of interest. Soluble Thy-1 will be measured in serum and correlated to inflammatory markers, chemokines, and relevant proteases.