

LTRC Concept Sheet # 09-99-0003

Chromatin Remodeling in the Regulation of Gene Expression in IPF

ABSTRACT

There is increasing evidence that gene regulation in humans is under epigenetic control. Epigenetics refers to heritable modifications to DNA structure, which are independent of the DNA sequence itself, and to their effects on gene transcription. These modifications include DNA methylation, histone modification, and chromatin remodeling. Chromatin is the polymeric structure into which DNA is folded in eukaryotic cells and changes in its structure (i.e., chromatin remodeling) can lead to the activation or silencing of genes by altering the accessibility of DNA to the cell's transcriptional machinery. Chromatin remodeling has been linked to both development and disease in multiple organ systems; however, little is known about the role of chromatin remodeling in lung disease.

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease of uncertain etiology that is associated with considerable morbidity and mortality. IPF affects the lung interstitium as well as the alveolar epithelium and is characterized by areas of fibrosis, activated fibroblasts, and honeycomb cysts alternating with areas of normal lung. Treatment options are limited and minimally effective. The median survival of patients with IPF is only three years, emphasizing the need for further scientific investigation.

The mechanisms involved in the pathogenesis of IPF remain incompletely characterized. Recently, chromatin remodeling has been implicated in the transforming growth factor-beta (TGF- β)-directed pathways involved in fibrosis. New data show that expression of brahma-related gene 1 (Brg1), a component of the BAF chromatin remodeling complex, is necessary for the expression of many genes activated by TGF- β , such as connective tissue growth factor. Additionally, chromatin remodeling has also been shown to mediate epithelial-mesenchymal transition, a process felt to play a role in scar formation and lung fibrosis.

The above findings lead to my hypotheses that chromatin remodeling genes are expressed in the lung and that chromatin remodeling is a mechanism of gene regulation which contributes to the pathologic phenotype of IPF. My goal is to further characterize the role chromatin remodeling plays in regulating genes known to be involved in fibrogenesis in the lung. This will be assessed by complementary approaches utilizing RNA and tissue provided through the Lung Tissue Research Consortium.

- (1) RNA from whole lung tissue will be used to characterize chromatin remodeling gene and TGF- β target gene activation in lung tissue from patients with a diagnosis of IPF using quantitative real time PCR;
- (2) Protein extraction/analyses of whole lung homogenates of freshly frozen isolated tissue will be used to measure chromatin remodeling protein expression in tissue obtained from patients with a diagnosis of IPF.