

LTRC Concept Sheet # 08-99-0036
The Influence of Gender on Molecular Signatures of Fibrotic Lung Disease

ABSTRACT

ABSTRACT: Idiopathic pulmonary fibrosis (IPF), the most common form of interstitial lung disease, is a chronic progressive disorder associated with extremely poor prognosis. There is currently no cure for IPF, and treatment options are relatively ineffective. Death from IPF continues to increase, with mortality rates significantly higher in men than women. Data from animal studies also reveal males are more susceptible to IPF. These observations infer that gender likely plays a significant role in the evolution of this disease. Despite research efforts, mechanisms underlying the pathogenesis of IPF are poorly understood and few studies have investigated the role of hormones and hormonal signaling pathways in IPF. The overall goal of this proposal is to determine the relationship between gene expression changes and disease severity and gender. Using lung tissues from patients diagnosed with IPF of varying severity (determined by FVC predicted), we will design a custom expression assay to measure the transcriptional profile of 47 gene targets simultaneously, 40 known to be important in disease development and/or pathogenesis as shown in animal and some human studies (nonsex/fibrotic genes) and 7 sex-related genes that may influence a gender-dependent association between gene expression profiles and severity of disease. Our overall hypothesis is that gender will influence gene expression levels for a subset of targets which vary with disease severity. We expect gender will influence sex-related gene expression signatures which are associated with non sex-related gene expression and further affect disease severity status. This hypothesis will be tested in the following 2 specific aims; (SA1) To measure the expression levels of 47 genes (sex-related and non sex-related/fibrotic genes) in lung tissue samples of patients diagnosed with IPF of various severity. To complete this aim, custom QRT-PCR assays will be developed and expression levels of these genes will be determined for each lung sample. (SA2) To develop and evaluate a two-stage statistical model to select target genes from 47 genes including sex-related and non sex-related, determine whether non-sex related gene expression levels vary by severity of IPF and gender, and further, whether sex-related genes indirectly affect non-sex related gene expression levels. Information gained from this work will provide invaluable information on (1) which genes, both sex and non sex-related, are altered in human patients; (2) Whether the effect of gender is mediated by hormonal receptor signaling on fibrotic genes; (3) Whether the effect of hormonal receptor signaling on IPF severity is mediated by fibrotic genes or is independent of the fibrotic genes that we investigate. Clarification of the molecular and cellular mechanisms that drive expression of critical genes involved in IPF will aid in establishing new or improved early disease biomarkers and enhancing therapeutic and prognostic strategies to treat incipient lung disease.