

LTRC Concept Sheet 08-99-0032
Proliferative and Apoptotic Studies in IPF Fibroblasts

Abstract:

Introduction and Background: Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease marked by an over abundance of myo-fibroblast cells within the diseased lung. These over-active myo-fibroblasts are instrumental in the deposition of excess extra-cellular matrix resulting in the fibrotic changes seen in the IPF lung. This fibrosis ultimately leads to the collapse of lung ultra-structure and terminal impairment in gas exchange. The source of the over-abundance of myo-fibroblasts in the IPF lung is unknown, however various theories propound, such as; increased proliferation, recruitment of precursor cells called fibrocytes, mesenchymal transitions of the resident epithelial cells, resistance to apoptosis after wound healing or all of these processes in parallel. The end-result is a fibrogenic environment, with distorted physiological architecture which leads ultimately to the failure of the lung's normal function and organ failure. These debilitating events place the fibroblast cells center stage in the pathology of IPF. Various theories have been developed surrounding the myo-fibroblast aimed at curing IPF by altering the fibroblast behavior. However the exact characteristics of IPF myo-fibroblast have yet to be determined due in part to the difficulty of isolation. Many of the previous IPF studies have been based on data generated from fibroblast cell lines and from primary fibroblast cells derived from long term outgrowths of IPF lung tissue. Both procedures result in a mixed population of cells with altered phenotype due to the mechanisms of isolation and long exposure to the tissue culture environment. However, the primary fibroblast cells used in the preliminary data generated for this study have been isolated by a novel method which is highly enriched for fibroblasts and bypasses some of the drawbacks of previous techniques. This results in cells with a phenotype closer to those seen *in vivo*. Microarray analyses and RT-PCR analyses have been conducted to identify altered behaviors in IPF fibroblasts compared to normal. However our data generated from the preliminary studies will benefit greatly from confirmation by immunohistochemistry analysis in IPF lung tissue, as well normal tissue. The data generated from this research project will help in our understanding, and potentially resolve the much debated issue of the proliferative and apoptotic profile of fibroblasts from IPF lung. Furthermore, the outcome of these studies will open opportunities which may be exploited for therapeutic intervention in future research efforts.

Aims: The overall objective of this research project is to determine the proliferative rate and sensitivity to apoptosis of pulmonary fibroblasts from the lungs of patients with Idiopathic Pulmonary Fibrosis (IPF) in comparison to normal pulmonary fibroblasts. The potential deregulated molecular pathways previously identified shall be confirmed in LRTC tissue samples.