Title: REGULATION OF MYOFIBROBLAST RESISTANCE TO APOPTOSIS BY ENDOTHELIN-1

Abstract

Pulmonary fibrosis is a progressive, debilitating disease process for which no effective therapy exists. The pathogenesis of pulmonary fibrosis involves a dysfunctional wound-repair response to acute or chronic/recurrent lung injury, resulting in myofibroblast activation and excessive extracellular matrix (ECM) accumulation. Studies have consistently shown that pulmonary fibrosis is characterized by aberrant mesenchymal and epithelial cell phenotypes.

Resolution of wound-repair requires coordinated spatial and temporal regulation of inflammatory and repair responses. Following injury, recruited mesenchymal cells differentiate into “effector” myofibroblasts which secrete ECM proteins that serve as a scaffold for reepithelialization. Myofibroblast apoptosis is crucial for the resolution of wound-repair and failure of myofibroblast apoptosis is associated with tissue fibrosis.

The cellular mechanisms regulating myofibroblast apoptosis in wound-repair are poorly understood. The pro-fibrotic cytokine, TGF-β1, induces myofibroblast resistance to apoptosis, in part, through the autocrine secretion of a soluble factor that activates PI3K/AKT. Endothelin-1 (ET-1) is a well characterized vasoactive peptide that has been shown to induce pro-fibrotic phenotypes including myofibroblast differentiation and ECM synthesis. Patients with pulmonary fibrosis have elevated levels of ET-1 and recent clinical trials support a role of ET-1 in the pathogenesis of pulmonary fibrosis. The effect of ET-1 on myofibroblast apoptosis remains undefined. We hypothesize that TGF-β1 induction of ET-1 by myofibroblasts leads to autocrine activation of PI3K/AKT and resistance to apoptosis. The goal of this proposal is to investigate the mechanisms regulating ET-1 expression in myofibroblasts and to define the role of ET-1 in myofibroblast resistance to apoptosis.