

ASP-CHEST FOUNDATION OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS GERIATRIC DEVELOPMENT RESEARCH AWARD



AWARD RECIPIENT

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PROJECT

"MYOFIBROBLAST FATE DETERMINATION BY EXTRACELLULAR MATRIX EVALUATIONS"

MENTORSHIP TEAM

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Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonias with an estimated prevalence of 89,000 cases in the United States. The incidence of IPF increases with age and the median survival rate is two to three years following the diagnosis. No pharmacologic intervention has been proven to impact mortality; traditional therapy, consisting of corticosteroids and immunosuppressive agents, presents an increased risk of complications in older adults. Although the pathogenic mechanisms of IPF remain unclear, the resulting fibrosis is thought to represent an aberrant wound-repair response to chronic or recurrent lung injury. Extracellular matrix (ECM) accumulation and remodeling lead to the loss of lung compliance and dyspnea are characteristic of this disease.

Myofibroblasts are necessary effectors of wound repair and are primarily responsible for secretion, organization, and contraction of ECM following injury. Myofibroblast fate is a critical determinant of wound-repair response resolution. Physiologic repair and maintenance of normal tissue architecture requires myofibroblast apoptosis and clearance of provisional ECM proteins, while inadequate myofibroblast apoptosis promotes continued ECM production, the destruction of tissue architecture, and the loss of tissue function. Our studies have focused on the mechanisms regulating myofibroblast survival.

We have previously defined several mechanisms by which the pro-fibrotic cytokine, transforming growth factor-beta 1 (TGF-1), promotes myofibroblast resistance to apoptosis, which forms the basis of our current research. We discovered TGF-1 promotes fibroblast survival through activation of focal adhesion kinase (FAK), a non-receptor tyrosine kinase. FAK is critical for the integration of physical signals from the ECM into biochemical signals within cells (mechanotransduction).

More recently, we discovered that plasminogen activation, which has been shown to prevent pulmonary fibrosis in animal models, promotes ECM degradation and fibroblast apoptosis. This degradation is reversed by TGF-1 mediated upregulation of the anti-protease, plasminogen activator inhibitor-1. The mechanism of plasminogen activation-induced fibroblast apoptosis has not been elucidated. In this research proposal, we hypothesize that ECM signals, transduced by FAK, are critical for fibroblast survival. Additionally, we propose that plasminogen activation-induced fibronectin proteolysis leads to the loss of pro-survival mechanotransduction signals, resulting in decreased FAK activity and myofibroblast apoptosis.

The goal of this project is to investigate the mechanisms by which mechanotransduction regulates fibroblast fate. This investigation will be pursued in three specific aims:

1. Investigate the regulation of plasminogen-mediated fibroblast apoptosis by FAK.
2. Determine how biomechanical tension regulates FAK activity and fibroblast susceptibility to apoptosis.
3. Examine the in vivo effects of plasminogen activation on fibronectin degradation and fibroblast apoptosis.

Through the support of the ASP-CHEST Foundation of the American College of Chest Physicians Geriatric Development Research Award, this research will enhance our understanding of the fundamental mechanisms of lung injury and repair that go awry in pulmonary fibrosis. Our long-term goals are to identify novel mechanisms that may be translated into therapeutic interventions for IPF. This award will facilitate the development of this topic into a novel area of independent investigation.