

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

Award Recipient:



ERIC S. WHITE, MD
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL

PROJECT:

THE ROLE OF FIBRONECTIN IN PULMONARY FIBROSIS

MENTORSHIP TEAM:

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*I*diopathic pulmonary fibrosis (IPF), a diffuse parenchymal lung disease for which there is no known effective therapy or cure, is a significant cause of morbidity and mortality in patients between the fifth and eighth decades. The disease is characterized by excessive deposition of the extracellular matrix proteins, collagen and fibronectin, and is thought to reflect a disordered wound healing response. The mainstay of therapy for patients with pulmonary fibrosis has been glucocorticoids, but this form of therapy is largely ineffective. Moreover, corticosteroid therapy at high doses in the elderly predisposes patients to increased risk of infection, osteoporosis and other musculoskeletal injury, alterations in mood, and exacerbations of comorbid conditions. While other therapeutic agents have been studied either alone or in combination with steroids, none has been found to slow the relentless progression of disease. Accordingly, new insights into the pathogenesis of IPF are necessary to develop more effective therapies while limiting toxicity.

Cellular fibronectin, produced by fibroblasts and macrophages during wound healing responses, is characterized by the inclusion of an alternatively-spliced domain termed EIIIA. This differs from plasma fibronectin, which lacks the EIIIA domain. Both plasma and cellular forms of fibronectin arise from the same fibronectin gene; generation of different fibronectin forms is thus tightly regulated, typical for a critically important determinant of cell function. Indeed, when regulation of fibronectin splicing is disrupted (in mice harboring constitutive inclusion or constitutive exclusion of the EIIIA exon of the fibronectin gene), lifespan is significantly shortened compared to wild-type animals. Interestingly, constitutive cellular fibronectin synthesis significantly increases with age, and appears to signify cellular senescence. Thus, in the setting of advanced age, if dysregulated fibronectin splicing resulting in excessive cellular fibronectin synthesis is associated with both cellular senescence and shortened lifespan, then one can envision a prominent role for fibronectin in the aging process. In

support of this possibility, degenerative disorders of the elderly, such as Alzheimer's disease, rheumatoid arthritis, and cataracts, have all been shown to be associated with increased, presumably inappropriate, fibronectin deposition.

In patients with IPF, cellular fibronectin is deposited in large quantities and localizes to the distorted fibrotic areas of the lung. While fibronectin deposition has been found to precede the development of experimental pulmonary fibrosis, if and/or how it actively contributes to fibrosis is unknown. Therefore, my research proposal encompasses the following goals:

To propagate a breeding colony of cellular fibronectin-null (EIIIA^{-/-}) and control EIIIA^{wt/wt} mice. These mice have been successfully generated in another laboratory and demonstrate an abnormal cutaneous wound healing response.

To evaluate whether the development of bleomycin-induced pulmonary fibrosis in mice is dependent on the presence of cellular fibronectin. Dissecting some of the cellular and biochemical events that might be regulated by cellular fibronectin and may contribute to pulmonary fibrosis, such as fibroblast proliferation, myofibroblast differentiation, and collagen secretion, will be a key part of this goal.

My academic development to date has included strong clinical and basic science training in pulmonary and critical care medicine at the University of Michigan Medical Center, where I currently hold a faculty position as assistant professor in the school of medicine. The ASP-CHEST Foundation Geriatric Development Research Award will allow me to continue pursuing the research endeavors I initiated during my fellowship with the ultimate goal of becoming an independent physician-scientist. Coupled with a mentored clinical scientist development award from the National Institutes of Health, I anticipate developing joint geriatrics and pulmonary clinical conferences as well as educational resources. Furthermore, this award will support new collaborations with other investigators in various fields to further delineate the role of cellular fibronectin in the pathophysiology of human disease.

