Fibrotic Nanofiber Scaffolds Mimic In Vivo Lung Microenvironment in Pulmonary Fibrosis

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Rationale: Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease of unknown origin that is characterized by irreversible scar tissue formation within the lungs. Collagen deposition, myofibroblast expansion, and the development of fibroblastic foci are hallmark pathological events that contribute to the scarring in IPF. The origin and mechanism of recruitment of myofibroblasts, the key cell leading to fibroblastic foci is unknown. We hypothesize that the fibrotic lung microenvironment causes the differentiation of bone marrow cells into myofibroblasts. In order to test this hypothesis, we have developed a novel method of studying the effects of the fibrotic microenvironment on various cell types through the utilization of nanofiber scaffolds.

Methods: Poly (e-caprolactone) nanofiber scaffolds were electrospun and coated with lung extracts from bleomycin or PBS-treated mouse lungs. Bone marrow cells were harvested from wild-type mice, plated on the nanofiber scaffolds, and allowed to expand. After various time-points, cells were observed by scanning electron microscopy and changes in fibrotic gene expression were determined by real-time PCR.

Results: Wild-type mouse bone marrow cells plated on the matrices coated with bleomycin-treated lung extract were observed by scanning electron microscopy to be secreting matrix materials and appearing more fibroblast-like after 8 and 14 days. These cells also had a significant increase in expression of the hallmark myofibroblast genes, type-I collagen and alpha-smooth muscle actin, as well as a significant increase in expression of connective tissue growth factor and tenascin-C.

Conclusions: These data underscore the importance of bone marrow derived cells in mediating pulmonary fibrosis. This ex vivo system recapitulates the three-dimensional fibrotic lung microenvironment, which will allow us to determine the cellular myofibroblast precursor and factors that regulate its differentiation, thus providing targets for promising new therapies.