

LTRC Concept Sheet # 09-99-0002
Mechanisms of Epithelial-Mesenchymal Transition in IPF

ABSTRACT

Epithelial-mesenchymal transition (EMT) is known to play a role in cellular transdifferentiation in development and in tumor invasion. Recent evidence suggests that myofibroblasts, key effector cells in the pathogenesis of idiopathic pulmonary fibrosis (IPF), may also be derived from alveolar epithelial cells (AEC) through EMT. However, mechanisms underlying EMT in this context are poorly understood. Transforming growth factor (TGF- β), implicated as a 'master switch' in induction of fibrosis, plays a pivotal role in EMT, and recent studies also suggest a role for activation of the Wnt/ β -catenin pathway in EMT. A demonstrated role for β -catenin signaling in EMT and IPF suggests that interactions between these two pathways may be a major factor mediating EMT in AEC.

The overall goal of this proposal is to investigate molecular mechanisms underlying EMT in AEC, focusing on crosstalk between TGF- β and Wnt/ β -catenin pathways. Our main hypotheses are: 1) EMT in AEC involves interactions between TGF- β and Wnt/ β -catenin pathways, 2) TGF- β -induced EMT in AEC is Smad-dependent and 3) modulation of EMT in AEC will provide new therapeutic approaches to management of patients with IPF. Lung tissue will be utilized to evaluate expression of downstream mediators in TGF- β (e.g. Smads) and β -catenin (e.g. LEF/TCF, GSK3- β , and β -catenin) pathways in AEC in IPF in order to investigate the role of these interactions in EMT and its relevance to human disease. Double-label immunofluorescence and RT-PCR will be performed with fixed tissue and RNA, respectively. Cell-specific expression of these downstream mediators will be evaluated by co-localization with epithelial and mesenchymal markers to determine expression in epithelial cells vs fibroblasts.