

LTRC Concept Sheet # 07-99-0005

Role of Heparan Sulfate 6-O-Endosulfatase 1 and 2 in Pulmonary Fibrosis

ABSTARCT

Transforming growth factor (TGF)- β 1 plays an important role in the pathobiology of pulmonary fibrosis (PF). One important property of TGF- β 1 is that it interacts strongly with heparin and highly sulfated heparan sulfate (HS). Importantly, heparin and HS potentiate TGF- β 1 function. Sulf1 and Sulf2 are the newly identified cell surface HS 6-O-endosulfatases, and have been shown to modulate HS-protein interactions by removing 6-O-sulfates from specific HS intra-chain sites. Preliminary studies in our laboratory reveal that TGF- β 1 induces both Sulf1 and Sulf2 expression in a mouse model of TGF- β 1-induced PF. In vitro, TGF- β 1 induces Sulf1 in primary normal human lung fibroblasts (NHLFs) and Sulf2 in A549 cells, which are adenocarcinoma cells derived from the alveolar type II epithelium. Furthermore, blocking the induction of Sulf1 or Sulf2 using siRNA in NHLFs and A549 cells, respectively, altered their responses to TGF- β 1. Based on our preliminary data, we propose to test the following hypothesis in this study: Heparan sulfate 6-O-endosulfatase 1 and 2 (Sulf1 and Sulf2) are involved in the pathogenesis of pulmonary fibrosis. The expression of Sulf1 and Sulf2 will be assessed by multiple and complementary approaches that utilize the IPF samples provided by the LTRC. First, the expression of Sulf1 and Sulf2 in freshly frozen IPF tissue samples will be assessed at both mRNA and protein levels using quantitative real-time reverse-transcription PCR and Western Blotting, respectively. Second, the expression and localization of Sulf1 and Sulf2 will be further analyzed in fixed tissue sections using in situ hybridization and immunohistochemistry. Finally, the expression data of Sulf1 and Sulf2 will be correlated with the histopathology and severity of the IPF samples. Findings from this study will reveal whether the expression of Sulf1 and Sulf2 are altered in the pathogenesis of IPF, and possible correlations between Sulf expression levels and IPF progression.