European Respiratory Society
Annual Congress 2013

Abstract Number: 1692

Publication Number: P470

Abstract Group: 1.5. Diffuse Parenchymal Lung Disease

Keyword 1: Idiopathic pulmonary fibrosis **Keyword 2:** Interstitial lung disease **Keyword 3:** Cell biology

Title: Uncoupling the pro-fibrotic effects of TGF-beta1 versus tissue hardening in lung fibroblasts

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Body: A hallmark of fibrotic interstitial lung diseases (ILDs) is the overabundance of activated fibroblasts. This activation can be induced by pro-fibrotic factors like TGF-b1. Intriguingly, recent studies support that extracellular hardening, which is another hallmark of lung fibrosis, is sufficient to induce many of the fibroblast alterations observed in ILDs. To unravel the effects of TGF-b1 from those of matrix rigidity, primary lung fibroblasts from either control (fibrosis-free) or patients (n=5-10) with fibrotic ILDs were cultured on polyacrylamide gels with rigidities comparable to normal or fibrotic lungs with TGF-b1, and their expression profilings were obtained with cDNA microarrays. Array data were normalized and filtered by computing the correlation between control and fibrotic samples for each probeset. A list of 12 and 7 genes was obtained for the normal- and fibrotic-like gels, respectively, and their classification power was assessed with KNN and PLSDA algorithms. Both lists successfully distinguished all the samples in the control and fibrotic groups. Interestingly, very few genes were common between normal- and fibrotic-like gels, including the F3 coagulation factor III gene. Array data revealed that F3 was highly expressed in fibrotic samples in both normal- and fibrotic-like rigidities, whereas it was downregulated in control samples in all conditions. These results reveal that F3 is abnormally upregulated in fibrotic fibroblasts, and strongly suggest that this upregulation is largely driven by TGF-b1 rather than by matrix rigidity, which may contribute to the hypercoagulable microenvironment in lung fibrosis.