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Title: The role of extracellular vesicles in phenotypic alteration of lung cells in pulmonary fibrosis

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Body: INTRODUCTION: Idiopathic pulmonary fibrosis is a disease of altered fibroblast-epithelial interaction. In response to stress lung fibroblast shed Thy-1 in the form of extracellular vesicles (EV). Exosomes are nano-sized vesicles that can be released from mesenchymal stem cells (MSC) as well. Supernatants from MSC, which contain EV have been shown to promote repair of neonatal lung injury. In this study we aimed to determine the role of EV in phenotypic modification of lung cells. METHODS: Exosomes were isolated from conditioned media of Thy-1(+) and Thy-1(-) rat lung fibroblasts (rfEV), respectively and human mesenchymal stem cells (hmEV) at baseline and after stimulation with Il-1-β and TNF-α. MSC were co-cultured with Thy-1(+) rfEV and Thy-1(-) rfEV. Rat lung fibroblasts (RLF) were cultured with hmEV. RNA was isolated from recipient cells. Species-specific primers were used to evaluate for the expression of myofibroblastic genes in hMSC and RLF. RESULTS: Cytokine-stimulated rfEV induced expression of α-smooth muscle actin, collagen 1, TGF-β and fibronectin-1 in hMSC. This process was independent of whether vesicles were Thy-1 (+) or (-). However, cytokine-stimulated hmEV suppressed expression of myofibroblastic genes by real time PCR in Thy-1(+) RLF. Nevertheless, in Thy-1(-) RLF cytokine-stimulated hmEV promoted myofibroblastic phenotype. Pretreatment of hmEV with RNase did not abolish in vitro effect of EV on target cell gene expression. CONCLUSIONS: RfEV promote acquisition of myofibroblastic genes in MSC in vitro. Effects of stimulated hmEV, released during inflammation can be either protective or detrimental, depending on Thy-1 characteristics of target lung fibroblast.