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Title: Pluripotent stem cells isolated from adult human lung tissue exhibit anti-fibrotic properties

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Body: Introduction: Dysregulated wound healing of the alveolar epithelium and increased proliferation of mesenchymal cells contribute to the development of pulmonary fibrosis. Hepatocyte growth factor (HGF) improved alveolar epithelial wound repair, and HGF-transfected bone marrow derived stromal cells reduced bleomycin-induced lung fibrosis in an animal model. We studied the role of HGF-expressing stem cells in the pathogenesis of lung fibrosis. Methods: Primary human stem cells were isolated from fibrotic lung parenchyma. The effect of stem cell-derived conditioned media (CM) on myofibroblast proliferation and on alveolar epithelial wound repair (using human A549 cells) was studied. Results: The pluripotency of the primary human stem cells was proven by positive stainings for Oct3/4 and NANOG. CXCR4 expression indicated the cells' bone marrow origin. Stem cell-derived CM exerted a significant anti-proliferative effect on primary human lung myofibroblasts (22% growth inhibition). Stem cells secreted HGF as demonstrated by ELISA. Compared to control medium, alveolar epithelial repair was markedly increased in the presence of stem cell-derived CM (+ 32%). This positive repair effect was abolished in the presence of neutralizing anti-HGF-antibodies. Conclusions: Our data demonstrate that CM obtained from bone marrow-derived lung resident stem cells inhibits the proliferation of myofibroblasts and enhances alveolar epithelium wound repair. Our data indicate that the anti-fibrotic effect is mediated via HGF. We hypothesize that HGF-expressing lung resident stem cells have fibro-protective properties and might therefore be a novel therapeutic approach for patients with idiopathic pulmonary fibrosis.