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Title: Cell cooperation between human fibrocytes and endothelial progenitor cells during neoangiogenesis is driven by the CXCR4 pathway

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Body: Idiopathic pulmonary fibrosis (IPF) is associated with a vascular remodeling process. Fibrocytes are a distinct population of blood-borne cells that coexpress hematopoietic cell antigens and fibroblast products, which have been shown to contribute to organ fibrosis. The purpose of this study was to test the hypothesis that fibrocytes may cooperate with endothelial progenitors to induce angiogenesis. We successfully isolated fibrocytes from blood of IPF patients. The characterization of fibrocytes used flow cytometry, real time q-PCR and confocal analysis. We investigated the interaction between fibrocytes and cord blood derived endothelial colony forming cells (ECFC) angiogenic potential in vitro and in vivo in a preclinical model of vascularization. We show for the first time the formation of functional microvascular beds in immunodeficient mice when human ECFC and fibrocytes isolated from IPF patients were co-implanted in matrigel plugs. Evaluation of implants after 2 weeks revealed an extensive network of blood vessels containing erythrocytes. Secreted media from fibrocytes enhances SDF-1/CXCR4 pathway in ECFC in vitro. Blocking CXCR4 in vivo in implants significantly inhibited blood vessel formation. Finally, we confirmed the relevance of these data by showing that vessels close to fibrotic areas in biopsy specimens from IPF patients expressed high levels of CXCR4, in contrast to control lungs. Circulating fibrocytes might be involved in vascular remodeling process observed in patients with fibrotic disease and should represent a useful biomarker for fibrosis progression.