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Title: Mast cells and fibroblasts work in concert to aggravate pulmonary fibrosis: Role of transmembrane SCF and PAR-2/PKCα/Raf-1/p44/42 signaling pathway

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Body: Mast cell (MC) accumulation has been demonstrated in the lungs of idiopathic pulmonary fibrosis (IPF) patients. Mediators released from MC may regulate tissue remodelling processes thereby, contributing to IPF pathogenesis. Here, we investigated the role of MC-fibroblast interaction for the progression of lung fibrosis. Increased number of activated MC, located in close proximity to fibroblast foci and alveolar type II cells, was observed in IPF lungs. Correspondingly, elevated tryptase levels were detected in IPF lung tissue samples. Co-culture of human lung MC with human lung fibroblasts (HLF) induced MC activation as evidenced by tryptase release, and stimulated HLF proliferation with IPF fibroblasts exhibiting a significantly higher growth rate compared to control fibroblasts. Tryptase stimulated HLF growth in a PAR-2/PKCα/Raf-1/p44/42 dependent manner and potentiated ECM production, however, independently of PKCα, Raf-1, and p44/42 activities. Proproliferative properties of tryptase were attenuated by knockdown or pharmacological inhibition of PAR-2, PKCα, Raf-1, or p44/42. Expression of transmembrane, but not soluble, SCF was elevated in IPF lung tissue and fibroblasts isolated from IPF lungs. Co-culture of IPF lung

fibroblasts with MC enhanced MC survival and proliferation. These effects were cell contact dependent and could be inhibited by application of anti-SCF antibody or CD117 inhibitor. Collectively, fibroblasts and MC appear to work in concert to perpetuate fibrotic processes and thus contribute to lung fibrosis progression.