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Oral Sessions

The role of vascular endothelial growth factor receptor 1 tyrosine kinase signaling in bleomycin-induced pulmonary fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) is a lethal lung disease with a poor prognosis. Fibroblast proliferation amplifies extracellular matrix deposition and increases angiogenesis. Vascular endothelial growth factor (VEGF) is one of the most potent angiogenic factors. VEGF interacts with VEGF receptors (VEGFR1 and VEGFR2). A previous study showed that VEGFR1 tyrosine kinase (TK) signaling induced blood flow recovery mediated by bone marrow (BM)-derived stem cells. We hypothesized that VEGFR1-TK signaling might be related to pulmonary fibrosis.

Material and methods: Six-week-old male C57Bl/6 wild-type (WT) mice and VEGFR1 TK knockout mice (TKKO mice) were treated with a single intratracheal injection of bleomycin (BLM; 0.1 μ g in 50 μ l saline) or vehicle (saline; 50 μ l). Lung fibrosis was evaluated by histology, real-time PCR and ELISA for pro-fibrotic factors, and assessment of lung mechanics.

Results: The fibrotic area in the lung and the lung elastance were significantly reduced in TKKO mice ($P < 0.01$). The expression of the fibrosis-related factors type I collagen, S100A4, and transforming growth factor (TGF)- β was also significantly reduced in TKKO mice on day 21 after BLM injection. TKKO mice also had significantly lower levels of stromal cell-derived factor (SDF)-1 in the lungs and plasma on days 14 and 21 after BLM treatment ($P < 0.05$). Moreover, the expression of C-X-C chemokine receptor type 7 (CXCR7) and CXCR4, the receptors for SDF-1, was also suppressed in TKKO mice. Immunohistochemical analysis showed that treatment with a CXCR4 antibody decreased the accumulation of VEGFR1+ cells in the lung in WT mice but not in TKKO mice.

Conclusion: These results suggest that VEGFR1 TK signaling promotes BLM-induced pulmonary fibrosis by activating the SDF-1/CXCR4 axis in infiltrating VEGFR1+ cells.