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Title: Inhibiting CXCR4/CXCL12 axis attenuates lung fibrosis both in vitro and in vivo

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Body: Background: Lung fibrosis is characterized by fibroblast proliferation and collagen deposition. CXCR4 chemokine receptor 4 (CXCR4), which binds the stromal cell-derived factor 1 (SDF-1)/CXCL12, has been shown a critical role in cell proliferation. Here, we aim to examine the exact modulatory effects of CXCR4/CXCL12 on the fibroblast proliferation and lung fibrosis. Methods: In vitro, primary human lung fibroblast (HLF) was isolated from patients with idiopathic pulmonary fibrosis and primary spontaneous pneumothorax for thoracoscopy with stapling of any air leak. CXCR4 protein level was assessed by indirect immunoblotting. MTT was used for the proliferation assay of bleomycin stimulated normal HLF in the presence or absence of AMD3100, an antagonist of CXCR4. In vivo, C57BL/6 mice were injected intraperitoneally with saline or AMD3100 (200ug) 1 day before intratracheal instillation of bleomycin (5mg/kg). Survival rate, lung fibrosis and pulmonary function will be assessed. Results: The basal level of CXCR4 expression was higher on fibrotic HLF. Bleomycin could promote the proliferation of normal HLF, which could be significantly attenuated by AMD3100 pretreatment. AMD3100 administration significantly increased the survival rate of mice on day 21 compared with bleomycin treatment alone. According to the histology, pulmonary fibrosis was attenuated by AMD3100 pretreatment in later stage of bleomycin injury. However, no significant differences in total lung capacity and airway resistance were observed between these groups. Conclusion: Collectively, our data suggest that AMD3100 could significantly attenuate lung fibrosis both in vitro and in vivo through inhibiting CXCR4/CXCL12 axis.