Therapeutic attenuation of silica-induced pulmonary fibrosis by immunotoxin chimeric molecule IL-13PE

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Rationale: IL-13 appears to contribute to the development of pulmonary fibrosis, presumably due to its ability to induce irreversibly fibroblasts activation, thus representing an attractive target in the case of fibrotic diseases. Inhalation of crystalline silica particles leads to silicosis, a chronic lung disease characterized by granulomatous inflammation and fibronodular response. Since there is no treatment that can effectively abolish the risk of the disease, in this study we examined the curative effect of the fusion protein IL-13PE on the experimental model of silica-induced pulmonary in mice.

Methods: Swiss-Webster mice were nasally instilled with silica particles (10 mg) and IL-13PE (500 ng/animal) was administered every other day, starting on day 21 up to day 28 after silica challenge. Twenty four hours later, pulmonary function and airways hyperreactivity to methacholine aerosolization were evaluated by invasive whole body plethysmography (FinePointe Buxco Platform). All animals were killed and whole lung samples were prepared for biochemical and histological analyses.

Results: Intranasal administration of IL-13PE had a significant therapeutic effect on increased pulmonary resistance and elastance as well as on airways hyperreactivity to the bronchoconstrictor agent methacholine in silicotic mice. IL-13PE also significantly reduced tissue fibrosis and granuloma formation. The levels of inflammatory and profibrotic cytokines (TGF-beta and TNF-alpha) and chemokines (MIP-2, JE and MIP-1alpha, TARC and MDC) as well as numbers of IL-13alpha2 receptor-positive cells, F4/80 positive cells and myofibroblasts in the lungs of silica-challenged mice were markedly suppressed by IL-13PE.

Conclusion: Our findings show that IL-13PE effectively inhibited silica-induced lung function failure, tissue fibrosis and granuloma formation, thus it may constitute a promising therapeutic approach in the case of chronic inflammatory diseases such as silicosis.

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