Role of Fas/FasL pathway mediated macrophage releasing inflammatory cytokines in human silicosis

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Abstract

**Objective:** Inflammatory cytokines play a key role in fibrosis in rodent animals. However, the mechanism of cytokine release by the AM of silicosis patients is unclear. The present study was to investigate the role of Fas/Fas ligand (FasL) in mediating alveolar macrophage derived inflammatory cytokines in human silicosis.

**Methods:** Twenty-nine silicosis patients and 6 controls with normal lung X-ray photography were selected for this study. AM obtained from whole lung lavage fluids of all subjects treated with anti-FasL antibody or caspase-8 inhibitor for 24 hours after purification. Six kinds of inflammatory cytokines and soluble Fas (sFas) were determined by enzyme-linked immunosorbent assay (ELISA). Membrane-bound Fas (mFas), caspase-8, and caspase-3 were detected by Western blotting and ELISA. AM apoptosis was detected by flow cytometry and DNA fragmentation analysis.

**Results:** The levels of the six kinds of cytokines in cultured AM supernatants from silicosis patients were higher than those of controls, and increased with the progression of silicosis except TGF-β1 and IL-8. IL-1β, TNF-α, IL-8, and MCP-1 were negatively correlated with duration of silica exposure, IL-1β and TNF-α were positively correlated with mFas, TGF-β1 was positively correlated with mFas, caspase-8, and caspase-3 in silicosis patients. mFas, Caspase-8 and -3, TGF-β1, IL-8, MCP-1, MIP-1α, and AM apoptosis were efficiently down-regulated by anti-FasL antibody and caspase-8 inhibitor.

**Conclusions:** Fas/FasL signaling serves to regulate the expression of inflammatory cytokines and to control the speed of lung fibrosis via inhibiting AM apoptosis.

**Keywords:** Fas/FasL pathway; Inflammatory cytokines; Alveolar macrophages; Apoptosis; Silicosis.

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