Cellular dynamics of fibroblasts and epithelial cells in chronic inflammation-associated organ fibrosis

MATSUSHIMA, Kouji

Professor, The Department of Molecular Preventive Medicine, The University of Tokyo, Tokyo, Japan

E-mail: koujim@m.u-tokyo.ac.jp

ABSTRACT

Organ fibrosis is an intractable, progressive condition that arises in multi-factorial chronic inflammatory diseases in which excessive deposition of extracellular matrix (ECM) severely impairs tissue architecture and function, eventually resulting in organ failure. The cellular origin and molecular bases for the accumulation of Col I-producing fibroblasts and myofibroblasts, which are responsible for the excessive deposition of ECM during the fibrotic process remain elusive.

Qualitative change, rather than quantitative change, is a hallmark of activated fibroblasts in bleomycin-induced lung fibrosis: Collagen I-producing fibroblasts were isolated from transgenic mice harboring enhancer/promoter sequences of α2(I) collagen gene linked to EGFP. Freshly isolated fibroblasts from bleomycin-treated mice had activated phenotype with the increase of collagen I expression and intracellular organelle complexity. These fibroblasts up-regulated expression of α-smooth muscle actin at day 7 and 14 but not 21 after bleomycin treatment. The number of fibroblasts in the whole lung did not increase even at the peak of fibrosis. Both proliferation and apoptosis of fibroblasts slightly increased when the inflammation progressed. We also analyzed gene expression profiles of normal and activated fibroblasts by a second generation DNA sequencer, identifying important signatures of activated fibroblasts including novel activation markers. These findings suggest that qualitative change, rather than quantitative change, is a hallmark of activated fibroblasts in bleomycin-induced lung fibrosis.

Fibrotic foci as the niches for migrating LRC in pulmonary repair: Slow-cycling label-retaining cells (LRCs) have been considered as putative stem/progenitor cell candidates in various organs/tissues. Homeostatic pulmonary LRCs exhibited several stem/progenitor-like characteristics including an immaturity, chemo/radiation-resistance and antioxidation, and formed the assemblies with alveolar progenitors, alveolar type 2 (AT2) cells, in the stroma-rich regions of the lungs. Upon challenge with bleomycin, these LRCs survived and accumulated at the fibrotic foci, which were surrounded by hyperplastic AT2 cells. In support, a variety of chemokine receptors were highly expressed on LRCs and their migration was inhibited by chemokine receptor antagonism. Our findings may suggest that fibrotic foci act as the niche for LRC in the repair process of the lung injury.